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Impact of Personality Profile on Patients with Obsessive Compulsive Disorder in an Egyptian Sample

Kamel M, Asaad T, Haroun El Rasheed A, Shaker N, and Abulmagd M

Abstract

Personality is manifest at all levels of the clinical practice in psychiatry. When discussing the etiology, diagnosis, assessment, management and outcome of any psychiatric disorder; the influence of personality status needs to be considered. Sporadic Egyptian studies estimated the prevalence rates of obsessive compulsive disorder (OCD) patients to be 2.6-3%, so this study was set out to assess personality in OCD, both as categorical personality disorders and as dimensional personality traits, and to explore the impact of personality factors on patients with OCD as regards the severity and expression of obsessive-compulsive symptoms, onset, course, duration, as well as the level of functioning and quality of life**.** This comparative study has enrolled 60 male and female patients aged over 18 years, with a primary diagnosis of OCD using DSM-IV-TR criteria, by convenient sampling. They were assessed using: 1. Structured Clinical Interview for DSM-IV-TR axis I disorders clinical version (SCID–I-CV) to diagnosis OCD and to exclude comorbid axis I disorders. 2. Medical and neurological history and examination to exclude concomitant medical or neurological illnesses. 3. Detailed history of the OCD condition. 4. Y-BOCS symptom checklist and Y-BOCS severity scale. 5. Structured Clinical Interview for DSM-IV-TR axis II disorders (SCID-II) scale. 6. Temperament and Character Inventory-Revised (TCI-R) scale. 7. Rotter Internal – External control scale. 8. Self-esteem scale. 9. PCASEE Quality of Life scale. 10. Global Assessment of Functioning scale (GAF). 11. Modified Social Score of Egyptian Community. Of the 60 OCD patients, 31 (51.7%) received one or more personality disorder (PD) diagnoses. Obsessive-compulsive personality disorder was the most frequently occurring PD in the OCD sample, however, with no specific relation between the two disorders. Presence of any cluster (B) PD was associated with higher symptoms severity. Presence of any cluster (A) PD suggested the presence of multiple PDs which in turn had a greater negative impact on many OCD features. Personality disorder comorbidity and the Self-Directedness character trait were the most important personality variables affecting almost all OCD features in the form of symptoms severity, expression, course, overall duration of the illness, time passed before initiating treatment, compliance, and most importantly, the functioning and quality of life of OCD patients. Lower scores of self-esteem and higher (external) locus of control scoring were associated with higher total Y-BOCS severity. The personality profile in the form of comorbid personality disorders, pathological temperament and character traits, self-esteem, and locus of control; besides their own pattern of significant clinical distress and impairment in social and occupational functioning; they have, in addition, a significant negative impact on the clinical characteristics of obsessive-compulsive disorder.

Introduction

Personality is manifest at all levels of the clinical practice of psychiatry. When discussing the etiology, diagnosis, assessment, management and outcome of any psychiatric disorder, the influence of personality status needs to be considered.

This is because a sufferer from mental disorder, whatever its nature, also has a personality, and its influence may be critical to understanding and treatment (Tyrer & Simonsen, 2003). Psychiatrists and other clinicians have often speculated on whether the presence of a personality disorder (PD) would have a specific influence on clinical picture and indicate a poorer course of treatment for an Axis I disorder? (Reich, 2003).

Obsessive-compulsive disorder (OCD) is considered the fourth most common psychiatric diagnosis after phobias, substance-related disorders, and major depressive disorder (Sadock & Sadock, 2003). Sporadic Egyptian studies estimated the prevalence rates of OCD to be 2.6% and 3% (Okasha et al., 1968 and El-Saadani, 1996 respectively). The economic consequences of OCD are wide-ranging, often long-lasting, and sometimes profound. They fall not only to the people with the disorder, but also to their families and-to a much lesser degree-to their society.

Personality disorders in general are present in approximately 50% of the psychiatric out-patients, and in 10-15% among the general population (Bodlund et al., 1993; Philips & Gunderson, 1999). In the case of OCD, Denys and his colleagues (2004) found that personality disorders are three times more prevalent in OCD patients than in general population. Moreover, OCD more often co-occur with a number of different personality disorders than, for instance, does panic disorder (Sciuto et al., 1991). The prevalence has varied from 33% to 87% depending on whether self-rating inventories or structured interviews have been used (Rasmussen & Tsuang, 1986; Joffe et al., 1988; Mavissakalian et al., 1990; Pfohl et al., 1991; Black et al., 1993; Thomsen & Mikkelsen, 1993; Baer & Jenike, 1998; Bejerot et al., 1998a; Matsunaga et al., 1998; Denys et al., 2004). Pigott and his colleagues (1994) concluded that over 50 percent of the OCD patients meet the criteria of at least one personality disorder.

Various explanations have been suggested to account for this comorbidity: (i) OCD predisposes to axis II disorders; (ii) axis II disorders predispose to OCD; or (iii) some environmental or biological risk factor, e.g. personality traits, predisposes to both OCD and personality disorders (Bejerot et al., 1998a).

OCD patients, compared to other non-psychotic patients, are more likely to receive a diagnosis from cluster A (the odd and eccentric cluster) (Pfohl et al., 1991). However, paranoid and schizoid as well as histrionic and antisocial personality disorders seem to be less prevalent in OCD patients than in the general population (Denys et al., 2004). Schizotypal features are present in up to 30 percent of the cases, although only approximately eight percent meet the full criteria for schizotypal personality disorder (Stanley et al., 1990).

The personality theory of Cloninger et al., 1993 is based on the biogenetic hypothesis of temperament and character which underlies patterns of human behavior and, thus, deserves an attention in the field of OCD research (Lyoo et al., 2003). The character traits are fluid (i.e., influenced by the environment). Therefore, they are the material that mental health professionals deal with and that deserve our attention.

Personality traits are always measured by dimensional approach which could be more useful in understanding such a

relationship as stated by Summerfeldt et al in 1998. Theorists from a variety of perspectives, including psychoanalytic (Salzman, 1980) and cognitive behavioral (McFall & Wollersheim, 1979), have asserted that obsessive-compulsives are highly perfectionistic and risk-aversive, and that these characteristics represent core aspects of the disturbance.

Lower scores on manipulativeness, mistrust, and disinhibition also distinguish the personality profile of OCD patients from others. Moreover, it is noteworthy that OCD patients show a pattern of very low self-image, as suggested by the combination of low self-esteem and low entitlement scores (Wu et al., 2005).

So, this study was set out to assess personality in patients with obsessive-compulsive disorder, both as categorical personality disorders and as dimensional personality traits, as well as to explore the impact of personality factors on patients with OCD as regards the severity and expression of obsessive-compulsive symptoms, onset, course, duration, as well as the level of functioning and quality of life.

Methods

Hypothesis:

The hypothesis of this study was that obsessive-compulsive disorder subjects would display differences in between them in specific personality constructs particularly, personality disorders; temperament and character traits; self-esteem; and locus of control. Moreover, this particular personality profile would have a negative impact on OCD features such as the severity and the expression of obsessive-compulsive symptoms, onset, course, duration, as well as the level of functioning and quality of life.

Subjects:

This comparative study has enrolled 60 OCD patients. The method of selecting subjects was done by convenient sampling. The study was conducted at outpatient clinics and inpatient departments of three centers in an attempt to cover different social classes. So, patients presented with obsessive-compulsive symptoms attending the Institute of Psychiatry, Ain Shams University on Sundays, Mondays and Thursdays were assessed; those attending the Nile Sanatorium were assessed on Saturdays and Tuesdays; and Psychological Medicine Hospital on Wednesdays.

Subjects meeting all criteria listed below were included in the study:

1. Male and female subjects aged over 18.
2. With a primary diagnosis of OCD, using DSM-IV-TR criteria.
3. Oral informed consent obtained.

Subjects presenting with any of the following were not included in the study:

1. Comorbid axis I DSM-IV-TR disorder during the past six months including alcohol or any other drug abuse.
2. Specific medical or neurological conditions that would interfere with the evaluation with the results of the study including: organic mental disease; mental retardation; history of psychosurgery; and history of epilepsy.
3. Unable to understand or implement the study procedures.

Tools:

All patients were assessed using the following tools:

1. Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I) Clinical Version (SCID-CV): (First et al.,1997)

SCID-I is a semi-structured interview for making the major DSM-IV Axis I diagnosis. It produces an efficient and user friendly instrument so that the advantages of structured interviewing could be applied in clinical settings. It is administered in a single sitting and takes 1 to 3 hours depending on the complexity of the psychiatric history and the skill and experience of the clinician. It is divided into seven diagnostic modules: Mood, Psychotic, Substance abuse, Anxiety, Somatoform, Eating and Adjustment disorders. The Arabic version used in this research was translated and used in previous Egyptian study (Shaker et al., 2003).

2. Yale-Brown Obsessive-compulsive Scale (Y-BOCS): (Goodman et al.,1989)

The Y-BOCS is a clinician administered semi-structured interview. It is considered the gold standard for assessing obsessive-compulsive symptoms. It is the best available measure of OCD severity. The interview is preceded by an optional 64 item checklist that is used to identify the content of obsessive-compulsive symptoms. Both obsessions and compulsions are rated in terms of time spent, interference with functioning, distress, resistance, and control. Rating of each aspect ranges from no symptoms (0) to extreme symptoms (4). Scores of Y-BOCS interview are summed to yield one total score and two subscales (obsessions and compulsions). Total score range from 0-40; higher scores indicate greater severity. Scoring of 10-20 indicates mild symptoms; 20-30 indicates moderate and 30-40 indicates severe symptoms. Administration time of the scale requires approximately 30 minutes. The Arabic version used in this research was translated and validated in many previous studies applied in the Institute of Psychiatry, Ain Shams University (Okasha et al., 1994).

3. Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II): (First et al., 1997)

SCID-II is a semi-structured interview that was developed to categorically and/or dimensionally assess the DSM-IV personality disorders. It could be used in both clinical as well as research settings. Items are organized by personality disorder. A 119-item yes/no screening questionnaire is available to reduce interview time by identifying personality disorders that are unlikely to be present. Each criterion is scored as 1=absent or false, 2=sub-threshold, 3=threshold or true, or? =inadequate information. Specific guidelines for a score of 3 (threshold) are provided. The average administration time is 20 minutes for the SCID-II screening questionnaire and just less than an hour for the SCID-II interview, when used in conjunction with the screen. The Arabic version used in this research was translated and used in a previous Egyptian study (Hatata et al., 2003).

4. Temperament and Character Inventory-Revised (TCI-R): (Cloninger et al., 1994)

The Temperament and Character Inventory-Revised is a self-report questionnaire that was used to measure biogenetic temperament and acquired character. It is suitable for administration

for adults (18 years and older); the mean administration time is 90-120 minutes. It consists of 240 items measuring the four basic dimensions of *Temperament* namely Novelty Seeking *(NS)*, Harm Avoidance *(HA)*, Reward Dependence *(RD)*, and Persistence *(PS)* and the three primary dimensions of *Character* namely Self-Directedness *(SD)*, Cooperativeness *(C)*, and Self-Transcendence *(ST)*. In this study, the responses were entered into a computer using the Statistical Package for Social Sciences-Version 13 (SPSS-13) program to score the test. The Arabic version used in this study was translated, validated and proved to be reliable in a previous Egyptian research work (El-Sheikh et al., 2003).

5. Self-esteem Scale: (El Dereni et al.,1982)

The self-esteem scale is an Arabic self-reported questionnaire designed to assess the overall self esteem of the reporter. It measures the self view of the reporter to his capabilities in different situations. It is composed of 30 items rated as follows: frequently=2, sometimes=1 and never=0. Items indicating low self esteem are inversely scored.

6. Rotter Internal – External Control Scale: (Rotter, 1966)

This self-administered instrument was designed to assess an important dimension of personality that is the locus of control. It evaluates the orientation of the person regarding external and internal reinforcements influencing his behavior. It indirectly explores the understanding of the person to his/her responses in different situations according to his/her belief in how far external forces affect his/her acts. Scoring of the scale is as follows: phrases pointing to the external locus of control score 1 point each, while those pointing to the internal locus of control score zero. The Arabic version used in this study was translated and validated by Kafafi (1982).

7. Global Assessment of Functioning (GAF) Scale: (Patterson and Lee, 1995)

GAF is a clinician-rated scale that was developed to rate axis-V of DSM-IV. It provides a measure of psychological, social and occupational functioning related to psychiatric symptoms.

8. The PCASEE Quality of Life Scale: (Beck et al., 1993)

The PCASEE quality of life scale (QoL) is a clinical instrument designed for interview administration, it provides information on symptoms and functioning over the last month. The 30-items are rated from 0-5. High scores reflect less impaired or unimpaired functioning and six domains are covered: (P) Physical component, (C) Cognitive component, (A) Affective component, (S) Social component, (E) Economic component, and (E) Ego functioning. The Arabic version used in this work was translated and validated in a previous Egyptian research study (Youssef et al., 2002).

9. Modified Social Score of Egyptian Community: (Fahmy and El- Sherbini, 1983)

This Arabic scale was proved to be a useful epidemiological tool as it reflects education, income values, health behavior and life style variables, all influencing the health status. It includes 5 items: education and occupation of the father, of the mother; monthly income; crowding index; and sanitation.

Procedures:

The research study was carried out through the period from September 2003 to December 2005 in which it passed through these stages:

A. Pilot Study:

A pilot study was conducted in the Institute of Psychiatry, Ain Shams University for four months (September–December 2003) prior to the start of the study proper.

Objectives of the Pilot Study:

1. To determine the size of the sample.

2. To assess the reliability of the diagnosis and ascertainment procedures.

3. To test the applicability and feasibility regarding time of administration and linguistic simplicity of the tools.

Results of the Pilot Study:

1. *Regarding determination of the sample size:* During the 4-months period of the pilot study, 38 patients were assessed. Only 10 patients were fulfilling the inclusion criteria. Accordingly it was decided to perform the study on a sample of 60 OCD patients during a period of 2 years.
2. *Regarding the reliability of the diagnosis and ascertainment procedures:* There was good conformity regarding the diagnosis between the psychiatrists in the outpatient clinics, a 3-year lecturer in psychiatry at the Institute of Psychiatry, Ain Shams University, and the clinical interviews done to the selected patients by the researchers of this work.
3. *Regarding the applicability and feasibility of the assessment tools:* The researchers had to give clear instructions and to clarify the questionnaires to patients participating in the research.

B. Study Proper:

The study proper was performed through the period from January 2004 to December 2005. After being informed of the purpose of the study, an informed verbal consent was obtained from all participants. They also provided verbal consent to the collection and release of data, and then the following procedures were performed:

1. Detailed psychiatric interviewing including full history and mental state examination, using Structured Clinical Interview for DSM-IV-TR axis I disorders (SCID–I) clinical version (SCID-CV).

2. Medical and neurological history and examination to exclude concomitant medical or neurological illnesses.

3. Detailed history of the OCD condition was taken including: age of onset, duration of illness, course, presence of stressor, time delay for seeking psychiatric help, and treatment compliance.

4. The profile of symptoms of OCD was clarified by Y-BOCS symptom checklist.

5. Assessment of OCD symptom severity was done by Y-BOCS for severity.

6. The profile of personality disorder comorbidity was clarified using the Structured Clinical Interview for DSM-IV-TR axis II disorders (SCID-II) scale.

7. Personality structure of participating patients was outlined using the Temperament and Character Inventory-Revised (TCI-R) scale.

8. The locus of control dimension was measured by Rotter Internal – External control scale.

9. Self-esteem of patients was evaluated using the Self- esteem scale.

10. Quality of life of patients was assessed by PCASEE QoL scale.

11. Functioning was assessed by the Global Assessment of Functioning scale (GAF).

12. Determination of social class was done according to the Modified Social Score of Egyptian Community.

The assessment of each patient was done through 2 to 3 settings. Each setting consumed around 1-2 hours according to the degree of cooperation of the patient and the complexity of findings obtained from the assessment.

During this period, 120 patients were assessed. Thirty-five were excluded because of the presence of comorbid axis I diagnosis (major depressive disorder, other anxiety disorders, psychotic disorders, and substance use disorders), 5 patients were excluded because of the presence of epilepsy. A total of 80 OCD patients were recruited. However, 20 of them (25% drop-out rate) dropped out from the study mostly because the assessment procedures were too long for them to fulfill (incomplete data were excluded). The remaining 60 subjects were enrolled in the study.

Statistical methods

All data were recorded and entered in a statistical package on a compatible computer. Analysis was done using an Epi Info ver.5 (2005).

Results

This study was carried out on 60 obsessive-compulsive disorder (OCD) patients recruited from outpatient clinics and inpatient departments of the Institute of Psychiatry, Ain Shams University; Psychological Medicine Hospital, Heliopolis; and the Nile Sanatorium, El-Maadi. Initially the study was carried on 80 patients, 20 (25%) subjects dropped out and the remaining 60 were enrolled in the study. Only 3 (5%) patients were hospitalized and 57 (95%) were collected from outpatient clinics.

I. Demographic Data of Patients:

The mean age of the sample was 30.4 (SD ± 8.8) years, whereas their age ranged from 18-51 years.

II. Impact of Comorbid Personality Disorder(s) on OCD:

To assess the impact of comorbid PD(s) on OCD, patients were divided into two groups: A group with comorbid PD(s) (N=31) and another group without comorbid PD (N=29). The two groups were compared to each other regarding the total Y-BOCS severity scoring, age of onset, duration of illness and time delay for seeking psychiatric treatment of OCD, Global Assessment of Functioning (GAF), the PCASEE Quality of Life scoring (QoL), and course of OCD, in addition to compliance on treatment.

1. Impact of Specific Types of Personality Disorder on Total Y-BOCS Severity:

Stepwise multiple regression analysis showed that dependent PD was significantly the most important PD affecting the total Y-BOCS severity ($F= 18.58$, $P<0.001$), followed by depressive PD ($F=7.49$, $P=0.01$), avoidant PD ($F= 7.03$, $P<0.05$) and borderline PD ($F= 7.01$, $P<0.05$).

2. Correlation between Specific Types of Personality Disorder and Type of Obsessions or Compulsions:

Ordering compulsions were positively correlated to passive aggressive PD (F= 8.42, P<0.01). There were significant positive correlations between sexual obsessions and schizotypal PD (F= 4.16, P=0.05), histrionic PD (F= 4.16, P=0.05) and antisocial PD (F= 4.16, P=0.05). Sexual obsessions were also positively correlated to narcissistic PD but not up to a statistically significant level (F=3.25, P>0.05).

Contamination obsessions were positively correlated to paranoid PD (F=2.19), aggressive obsessions were negatively correlated to borderline PD (F=2.61), and positively correlated to OCPD (F=2.61), hoarding was positively correlated to avoidant PD (F=3.45), however, these correlations were not reaching the point of statistical significance (P>0.05).

III. Impact of Personality Traits on OCD

1. Correlation between Personality Traits and Total Y-BOCS Severity:

There were highly significant negative correlations between SD and C and total Y-BOCS severity (P<0.01), i.e., lower SD and C scores were associated with higher total Y-BOCS severity scoring. There was an only significant positive correlation between HA and total Y-BOCS severity (P=0.05), i.e., higher HA scoring was associated with higher total Y-BOCS severity scoring.

A negative correlation was found between RD and total Y-BOCS severity. On the other hand, positive correlations were found between NS, PS, ST and total Y-BOCS severity. However, these correlations were not reaching the point of statistical significance (P>0.05). On the contrary, there was negative correlation between NS1 subscale and total YBOCS severity scoring, low scores on the NS1 (exploratory excitability vs. stoic rigidity) subscale, suggest that these subjects prefer familiar situations and tend to resist new ideas, also this correlation was not reaching the point of statistical significance (P>0.05).

Stepwise multiple regression analysis showed that SD was significantly the most important personality trait affecting total Y-BOCS severity (F=5.22, P<0.05) followed by C (F= 2.89) and PS (F=1.23), but both were without statistical significance (P>0.05).

2. Correlation between Personality Traits and Symptom Expression of OCD:

A significant negative correlation was found between C (F=8.25, P<0.01), SD (F=5.54, P<0.05) and obsessions severity, i.e., lower SD and C scoring were associated with higher obsessions severity. No other correlations were found between other personality traits and obsessions or compulsions severity.

3. Impact of Personality Traits on Course of OCD:

To assess the impact of personality traits on course of OCD, patients with continuous and progressive course (poor prognosis) were compared to patients with episodic and improving course (good prognosis) regarding the mean scores of TCI personality traits. Patients with remissions and exacerbations course (natural course of the illness) were excluded from the comparison.

Patients with continuous and progressive course had significantly lower mean scores of SD (P<0.001), RD (P<0.01) and C (P<0.05) than those with episodic and improving course. On the other hand, the former group of patients had higher mean scores of NS, HA and ST and lower mean score of PS, however without statistically significant difference than the latter group of patients (P>0.05).

Stepwise regression analysis revealed that C was significantly the most important personality trait affecting the course of OCD (F=4.38, P<0.05) followed by SD (F=1.28, P>0.05).

4. Correlation between Personality Traits and Duration of OCD:

SD and NS were negatively correlated to the overall duration of OCD (F=8.06, P< 0.01; F=2.78, P>0.05 respectively), while HA and ST were positively correlated to the overall duration of OCD (F=3.89, P=0.05; F=3.46, P>0.05 respectively). Other personality traits had no correlation with the overall duration of OCD. Stepwise multiple regression analysis revealed that SD was significantly the most important personality trait affecting the overall duration of OCD (F= 4.09, P<0.05) followed by NS and ST (F=2.88, P>0.05; and F=0.89, P>0.05 respectively).

5. Correlation between Personality Traits and Time Delay for Seeking Treatment of OCD:

SD was negatively correlated to time delay for seeking treatment of OCD (P<0.05). So, lower SD scores were significantly associated with longer time delay for seeking treatment of OCD. Also, NS was negatively correlated to time delay for seeking treatment of OCD without reaching the point of statistical significance (P>0.05). There were positive correlations between HA, RD, ST and time delay for seeking treatment of OCD without reaching the point of statistical significance (P>0.05). Stepwise multiple regression analysis showed that SD was significantly the most important personality trait affecting the time delay for seeking treatment of OCD (F=5.31, P<0.05) followed by RD (F=1.94, P>0.05) and NS (F=1.01, P>0.05).

6. Impact of Personality Traits on Compliance on Treatment of OCD:

Non-compliant patients had significantly lower mean scores of SD (t=2.9, P<0.01) and RD (t=2.1, P<0.05) than compliant patients. Also, non-compliant patients had higher NS (t=0.3), HA (t=1.3) and ST (t=1.6), lower C (t=0.7) and PS (t=0.9) mean scores, however, without statistically significant difference from compliant patients (P>0.05). Stepwise multiple regression analysis revealed that SD was significantly the most important personality trait affecting compliance (F=8.4, P=0.01) followed by RD (F=1.99, P>0.05).

7. Correlation between Personality Traits and Global Assessment of Functioning:

There were significant positive correlations between SD (P<0.001), C (P<0.01) and GAF (i.e., low SD and C scores were significantly associated with low GAF scoring). On the contrary, there were significant negative correlations between HA (P=0.01), ST (P<0.01) and GAF. i.e. higher HA and ST scoring were significantly associated with low GAF scoring. RD was positively correlated to GAF, however not reaching the point of statistical significance (P>0.05). Stepwise

multiple regression analysis showed that SD is significantly the most important personality trait affecting GAF (F=9.57, P<0.01) followed by C (F=2.86, P>0.05).

8. Correlation between Personality Traits and Quality of Life:

SD, PS and C were positively correlated to QoL scoring with variable statistical significance (P<0.001, P=0.01, P<0.05 respectively). On the other hand, there was a highly significant negative correlation between HA and QoL scoring (P<0.001). RD was positively correlated to QoL scoring, ST was negatively correlated to QoL scoring, however, not reaching the point of statistical significance (P>0.05). Stepwise multiple regression analysis revealed that SD was significantly the most important personality trait affecting QoL (F=61.76, P<0.001) followed by PS (F=2.76, P>0.05).

IV. Impact of Self-esteem on OCD

There was a highly significant negative correlation between self-esteem and total Y-BOCS severity (P<0.001). Lower scores of self-esteem were associated with higher total Y-BOCS severity. There was a highly significant negative correlation between self-esteem and obsessions severity (P<0.001). i.e. lower scores of self-esteem were associated with higher scores of obsessions severity. However, there was no correlation between self-esteem and compulsions severity.

Series of correlation tests were done to assess the self-esteem and age of onset, duration of illness, and time delay for seeking treatment of OCD, Global Assessment of Functioning, and PCASEE quality of life scoring:

- There were highly significant positive correlations between self-esteem, GAF and QoL scoring (P<0.001) (i.e., higher self-esteem is associated with higher GAF and QoL scoring).
- On the other hand, self-esteem was negatively correlated to the duration of illness and time delay for seeking treatment of OCD (i.e., lower self-esteem was associated with longer duration of illness and longer time delay for seeking treatment of OCD), without reaching the point of statistical significance (P>0.05).
- There was positive correlation between self-esteem and age of onset of OCD, however, not up to statistically significant level (P>0.05).

Comparative study between mean self-esteem scores of patients with continuous and progressive course (poor prognosis) and patients with episodic and improving course (good prognosis) of OCD revealed that the former had significantly lower self-esteem scoring than the later (P<0.001). Moreover, non-compliant OCD patients on treatment had significantly lower self-esteem than compliant patients (P<0.001).

V. Impact of Locus of Control on OCD

There was a highly significant positive correlation between locus of control and total Y-BOCS severity (P<0.001) [i.e., higher locus of control scoring (more towards external locus of control) was significantly associated with higher Y-BOCS severity].

Locus of control was positively correlated to compulsions severity (P<0.001) [i.e., higher locus of control (more towards external locus of control) was associated with higher compulsions severity]. There

was no correlation between locus of control and obsessions severity.

There was a highly significant negative correlations between locus of control and GAF as well as QoL scoring (P=0.001) [i.e., higher locus of control scoring (more towards external locus of control) was significantly associated with lower GAF and QoL scorings]. Locus of control was positively correlated to age of onset, duration of illness and time delay for seeking treatment of OCD [i.e., higher locus of control scores (more towards external locus of control) was associated with older age of onset, longer duration of illness and longer time delay for seeking treatment of OCD], however, it did not reach the point of statistical significance (P>0.05).

On comparing the mean locus of control scoring of patients with continuous and progressive course (poor prognosis) to those with episodic and improving course (good prognosis) of OCD, the former group of patients had significantly higher mean locus of control scoring (more towards external locus of control) (P<0.001) than the latter group. Moreover, non-compliant OCD patients had significantly higher locus of control (more towards external locus of control) mean scores (P<0.001) than compliant patients.

Table (1): Frequency of Different Types of Personality Disorder among OCD Patients

Type of Personality Disorders	N=60	%
Any Cluster A	6	10%
Paranoid	5	8.3%
Schizotypal	2	3.3%
Schizoid	1	1.7%
Any Cluster B	8	13.3%
Histrionic	2	3.3%
Narcissistic	4	6.7%
Borderline	7	**11.7%**
Antisocial	2	3.3%
Any Cluster C	28	**46.7%**
Avoidant	11	**18.3%**
Dependent	6	10%
Obsessive-Compulsive	24	**40%**
Not Otherwise Specified (NOS)	12	20%
Passive-aggressive*	6	10%
Depressive	8	**13.3%**
Any Personality Disorder	31	51.7%
No Personality Disorder	29	48.3%

- N indicates number; * also called negativistic personality disorder in DSM-IV-TR.

Table (2): Impact of Comorbid Personality Disorder on Clinical Features of OCD Patients

Clinical Features of OCD	Patients with PD (31)		Patients with no PD (29)		*t*	P
	Mean	± SD	Mean	± SD		
Y-BOCS Severity	30.13	± 6.5	20.76	±5.7	5.9	**0.000*** **
Age of Onset	21.1	±8.4	22.24	±5.9	0.6	0.5
Duration (years)	9.73	±7.6	6.8	±6.3	1.6	0.1
Time Delay for Treatment (years)	6.09	±6.1	4.81	±9.9	0.8	0.3
GAF Scoring	47.1	± 7.6	60.66	±4.8	8.2	**0.000*** **
QoL Scoring	41.74	±20.5	59.97	±18.2	3.6	**0.001*** **

*** indicates very highly significant data (P≤0.001); (P>0.05) non significant; OCD, obsessive-compulsive disorder; PD, personality disorder; Y-BOCS, Yale-Brown obsessive-compulsive scale; GAF, global assessment of functioning scale; QoL, quality of life scale.

Table (3): Impact of Number of Personality Disorder on Clinical Features of OCD

Clinical Features of OCD	Single PD (14)		Multiple PDs (17)		*t*	P
	Mean	±SD	Mean	±SD		
Y-BOCS Severity	26.5	±8.4	33.1	±5.9	3.2	**0.003** **
Age of Onset	19.86	±5.9	22.12	±10.1	0.7	0.5
Duration (year)	9.46	±8.2	9.94	±7.25	1.5	0.4
Time Delay for Treatment (year)	6.36	±7.8	5.89	±4.25	0.8	0.2
GAF Scoring	52.07	± 6.3	43.0	±6.01	4.1	**0.000*** **
QoL Scoring	55.14	±17.6	30.71	±15.8	4.1	**0.000*** **

** indicates highly significant data (P≤0.01); *** very highly significant (P≤0.001); (P>0.05) non significant; OCD, obsessive-compulsive disorder; PD, personality disorder; Y-BOCS, Yale-Brown obsessive-compulsive scale; GAF, global assessment of functioning scale; QoL, quality of life scale.

Table (4): Impact of Personality Traits on Course of OCD

Personality Trait	Continuous, Progressive Course		Episodic, Improving Course		*t*	P
	Mean	±SD	Mean	± SD		
NS	99.32	±9.97	94.65	±12.07	1.5	0.2
HA	114.0	±15.6	111.2	±17.8	1.5	0.2
RD	101.14	±13.8	108.2	±12.7	2.1	**0.005****
PS	115.1	±18.5	119.6	±21.9	1.6	0.3
SD	117.96	±19.5	136.1	±25.4	2.5	**0.000*****
C	124.05	±10.6	130.2	±4.1	2.0	**0.03***
ST	78.14	±18.2	72.12	±13.48	1.5	0.2

* indicates significant data (P≤0.05), ** highly significant (P≤0.01); *** very highly significant (P≤0.001); (P>0.05) non significant; NS, novelty seeking; HA, harm avoidance; RD, reward dependence; PS, persistence; SD, self-directedness; C, cooperativeness; ST, self-transcendence

Discussion

Obsessive-compulsive disorder (OCD) is a common and disabling psychiatric condition that affects both children and adults (Cruz-Fuentes et al., 2004). Over the years, clinicians have described a number of abnormal personality traits in the affected individuals. The coexistence of axis II personality disorder (PD) is frequently reported. Only in the past decade have the personality features of OCD patients been systematically evaluated from the perspective of different theoretical models (Lyoo et al., 2001). The research literature on categorically defined personality disorders (PDs) in OCD has been relatively fruitless so far and several investigators have posited that a dimensional approach could be more useful in understanding such a relationship (Summerfeldt et al., 1998).

However, little is known about differences in clinical characteristics between OCD patients with and without comorbid symptoms suggesting PD(s) or personality traits. Accordingly, the aim of the present study was to assess personality in patients with a primary diagnosis of OCD, both as categorical PDs, and as dimensional personality traits, and to explore the impact of personality factors on the clinical characteristics of OCD patients.

Patients suffering from OCD in this study were compared among themselves, regarding their personality profile (PDs, personality traits as measured by the temperament and character dimensions, the self-esteem, and the locus of control). Personality profile of OCD patients was assessed as an independent variable in different ways, corresponding to the research questions: (1) the presence of any PD vs. no PD, (2) presence of individual PD, (3) presence of any cluster PD(s), (4) the total number of PDs, (5) impact of PD(s), temperament and character traits, self-esteem, and locus of control on OCD

patients regarding the following: Y-BOCS severity, symptom expression, age of onset, course, overall duration, time delay for seeking treatment and compliance on treatment, as well as overall functioning and quality of life of OCD patients.

In our study, mean time delay for seeking psychiatric help was 5.5 years. Jenike in 2001 reported a 5-10 years delay before OCD patients come to psychiatric attention. He attributed this to the fact that those patients tend to keep their symptoms secret. The mean overall duration of illness in subjects of the current study was found to be 8.4 years.

Only half of the subjects of this work presented with combined obsessions and compulsions. The remaining half showed that the predominantly obsessive type was slightly more than double the number of that of the predominantly compulsive type (n=21:10).

Impact of Comorbid Personality Disorder(s) on OCD:

There was a high frequency of comorbidity with PDs as 51.7% of the subjects with OCD had at least one PD according to the self-report SCID-II questionnaire. This finding is consistent with previous investigators' results over the past two decades who have reported prevalence rates of clinically significant PDs in the OCD population. Baer et al., 1992 found that 60% of their OCD patients received one or more PD diagnoses. Bejerot and her colleagues, 1998a concluded that 75% of their OCD patients received at least one diagnosis of a PD, while Denys and his team in 2004 found that only 36% of their OCD sample received one or more PD diagnoses. Generally, in many other studies, the reported prevalence rate was significant (33%-87%) irrespective of whether self-rating inventories or structured interviews were used (Joffe et al., 1988; Mavissakalian et al., 1990; Black et al., 1993).

It was found that 23.3% of the subjects in this work had a single PD, while 28.3% had 2 or more PDs up to a maximum of 8. The most prevalent PDs were obsessive-compulsive PD (OCPD) (40%), and avoidant PD (18.3%). Cluster (C) PD occurred most frequently (46.7%). On the other hand, the least frequent PDs were antisocial PD, histrionic PD, schizotypal PD (3.3% for each), and schizoid PD (1.7%). Paranoid PD occurred as a modest of (8.3%) of this sample.

Baer et al., 1992 and Steketee in 1999 found that the avoidant, dependent, and passive-aggressive PDs were the most commonly present in OCD patients. They also found that most PD diagnoses were in the cluster (C) group. Bejerot et al., 1998a largely concluded the same results as the present study regarding OCPD which occurred in (36%) of their sample. Again cluster (C) PD was the most prevalent cluster (55%). Also, the most infrequent PDs in their study were histrionic PD (6%), followed by schizotypal and schizoid PDs (3%). However, avoidant and paranoid PDs were found in (31%). Recently, Denys et al., 2004 found that the most prevalent PD in their sample was also the OCPD, followed by dependent PD and then PD not otherwise specified. The most infrequent PDs were antisocial, paranoid, and schizoid PDs. Cluster (C) PD was also the most frequent occurring cluster in their study.

Compared to these studies examining PDs, the prevalence rates in the present sample were by and large equivalent to the

reported prevalence rates; except for paranoid PD in this sample which was found in sharp contrast with Bejerot et al., 1998a report; 8.3% compared to 31% respectively. An Egyptian study conducted by Okasha and coworkers in 1996 suggested that OCD and OCPD seem to be related. However, among the cases with OCPD in our study, the majority appeared together with other PDs, a finding which seems to argue against such a specific relationship.

Consistent with prediction, OCD patients primarily displaying comorbidity with any PD versus those with no PD differed significantly in many OCD-related domains. The results of this study revealed the following: patients with comorbid any PD had significantly higher total Y-BOCS severity scoring than those without comorbid PD. In addition, patients with comorbid PD were significantly less functioning with significantly worse QoL than those without PD. The inflexible pattern of thoughts and actions found in personality disordered OCD patients may account for the higher severity of symptoms compared to those without PDs. Moreover, the impaired social and occupational functioning of a personality disordered persons may add to the lower levels of functioning seen among them compared to those with no axis II disorders.

The analysis also revealed that 70% of patients with PD(s) had continuous or progressive (poor prognosis) course while only 30% had episodic or improving course and this difference was statistically significant ($P<0.05$). Among the non compliant patients, there was significantly ($P<0.05$) higher percentage of patients with comorbid PD (76.5%) than those without PD (23.5%). OCD patients with comorbid PD were found to have longer overall duration and longer mean time delay for seeking psychiatric treatment than those without PDs, yet without statistical significance. It was stated by Sadock and Sadock in 2003 that persons with PD(s) are far more likely to refuse psychiatric help and deny their problems than persons with OCD alone. Thus, those with comorbid PD(s) are more prone to present with longer time before seeking psychiatric help, show less favorable course and are non-compliant on treatment.

The concluded clinical observations from some studies (Hoffart, 1994; Hofmann et al., 1998) suggest that the negative effect of personality on short-term outcome may have resulted from some patients' slower and more cautious engagement in therapy (i.e. longer time delay for seeking treatment). Personality disordered patients were quite ambivalent about changing avoidant and ritualistic behaviors that had maintained their anxiety problems.

Denys et al., 2004 found that patients with comorbid PDs were to a higher extent impaired in overall functioning. Other studies, however, suggest that early onset of OCD, long overall duration of illness or high scores on the Y-BOCS showed no association with the frequency or number of PDs *(*Steketee et al., 2001). Presence of a PD per se was unrelated to the outcome on OCD scales; this was concluded by Baer et al in 1992.

Cluster (B) PDs (antisocial, borderline, histrionic, narcissistic) was significantly the most important cluster affecting the total Y-BOCS severity ($P=0.01$) in this sample, followed by PDs NOS (passive-aggressive and depressive) ($P=0.03$). Cluster (A) PDs (paranoid, schizoid,

schizotypal) also had an effect on Y-BOCS severity, however, without reaching a statistical significance. Cluster (C) PDs (avoidant, dependent, obsessive-compulsive) although they were represented as the most prevalent cluster in this sample, yet they were not significant regarding their impact on total Y-BOCS severity of the OCD patients.

Patients with any cluster (B) PD are considered to be dramatizing most of their reactions; this may be manifested in giving higher scores on the Y-BOCS severity scale (i.e. dramatizing severity). Moreover, their impulsive nature may drive them to yield easily to compulsions which also may account for the greater severity seen in those patients with cluster (B).

In the current study, presence of any cluster (A) PD was always associated with at least another PD. Patients with more than one PD had more severe form of OCD, poorer course, less overall functioning, and worse QoL. Thereby, the presence of any cluster (A) PD could be an indirect cause of less favorable characteristics of OCD.

Baer et al., 1992 found that there was a strong relation between the presence of at least one cluster (A) PD and the total number of PDs diagnosed. Also, number of PDs and the presence of a cluster (A) (or cluster B) disorder were related to OCD severity. Results of many researchers were almost similar in this issue and lend further support to the claim that schizotypal symptoms dispose to a negative treatment outcome (Minichiello et al., 1987; de Haan et al., 1997; Moritz et al., 2004).

Regarding the impact of specific types of PDs on OCD severity, stepwise multiple regression analysis showed that dependent PD was significantly the most important PD affecting the total Y-BOCS severity in this sample, followed by depressive, avoidant, and borderline PDs.

Interestingly, dependent personalities show poor compliance on behavioral therapies (as exposure response prevention) but not on pharmacotherapy. People with dependent personality features tend to believe that medications would improve everything regarding their illness, and they completely *depend* on them. They do not want to do any extra effort in behavioral therapy as long as there is a medication that would do the whole job.

Impact of Personality Traits on OCD

Personality traits may play a role in treatment seeking behaviors for mental health problems over and above the presence of psychiatric disorder alone. The assessment of relevant personality constructs has the potential to inform and improve treatment outbreach efforts (McWilliams et al, 2006):

1) Novelty Seeking (NS)

There were positive correlations between the temperament trait of total (NS) and total Y-BOCS severity scorings, however, without reaching the point of statistical significance. Interestingly, (NS1) subscale was found to be negatively associated with the severity, however, without reaching the point of statistical significance. Low scores on the (NS1) (exploratory excitability vs. stoic rigidity) subscale, suggest that these subjects prefer familiar situations and tend to resist new ideas. Low (NS1) traits are characterized by stable unwillingness to consider new or unconventional ideas and closed-mindedness, may be specifically associated with obsessions. Also, stable unwillingness to try different activities and

preference for routine and familiarity, may be specifically associated with compulsions (Cloninger et al., 1994).

2) Harm Avoidance (HA)

There was a significant positive correlation between (HA) temperament trait and total Y-BOCS severity in the present results. Higher scores of (HA) were also significantly correlated to longer overall duration of illness, less functioning and worse QoL compared to those with lower scores of (HA). Lyoo and colleagues, 2001 reports were in agreement with the current study's results, they indicated that high (HA) scores had a significant relationship with the severity of OCD symptoms. No significant correlations were found between (HA) and the OC symptoms expression, age of onset, course, and time delay for seeking treatment of OCD or the compliance on treatment.

3) Reward Dependence (RD)

Patients with continuous and progressive course had significantly lower (RD) mean scores than those with episodic and improving course. Non-compliant patients had significantly lower scores of (RD) than compliant patients. Low (RD); together with low (NS), and high (HA); were described as being an *obsessional* temperamental type as concluded by Cloninger and colleagues in 1994.

4) Persistence (PS)

Lower mean scores on the (PS) temperament trait was significantly correlated to worse QoL in OCD patients. Less compliant patients had lower mean scores of (PS), however, without reaching the level of statistical significance. Cloninger and colleagues in 1994 described those with low scores of (PS) as individuals with poor achievements; they tend to give up easily when expectations are not quickly satisfied or when faced with criticism, obstacles, fatigue, or frustrations. They typically have problems in starting or finishing work and rarely exhibit their best efforts even in response to anticipated reward. Thus, their resistance to obsessional thoughts, carried out compulsions, as well as their compliance on treatment regimen will be lowered. These traits may contribute to the worse QoL seen in patients with lower (PS) scores.

5) Self-Directedness (SD)

The character trait of ***Self-Directedness*** was the most significant personality trait that was found to have an impact on almost all OCD features. Results indicate that low (SD) scores have a significant relationship with the severity of OCD symptoms i.e. greater severity of obsessive-compulsive symptoms is, in part, explained by the low (SD) of the biogenetic character of subjects with OCD. This particular finding is in agreement with previous reports in Korea by Lyoo and colleagues in 2001 and in Mexico by Cruz-Fuentes and colleagues in 2004. They identified a similar inverse effect for this particular character dimension on the Y-BOCS total scores.

Stepwise multiple regression analyses showed that (SD) generally is the most important personality trait affecting OCD variables including the following: total Y-BOCS severity; obsessional severity; overall duration of illness; time delay for seeking treatment; compliance on treatment; GAF; and QoL.

6) Cooperativeness (C)

There was a significant negative correlation between (C) character

dimension and the total Y-BOCS and obsessional severity. Low Cooperativeness is characteristic of many people who prefer to be solitary, which may explain the high obsessions severity in them. Low (C) and (SD) character dimensions were reported in Svrakic and his colleagues' works in 1993 to be core features of all personality disorders. This relation between low (C) and (SD) and the presence of PDs may explain the poorer level of functioning and the worse QoL seen in those OCD patients who exhibit lower scores of (SD).

7) Self-Transcendence (ST)

Higher (ST) scores were significantly correlated to lower GAF. The (ST) character trait had no significant correlations to the following variables: total Y-BOCS severity, OC symptoms expression, age of onset, course, overall duration, time delay for seeking treatment of OCD, compliance on treatment, and QOL. Interestingly, a very recent study done in Japan by Matsudaira and Kitamura in 2006 revealed that specific anxiety was predicted by higher (NS), (HA), and (ST), and lower (SD). These findings are very much in agreement with the findings of the current study that showed similar parameters on the same personality traits in the anxiety-related OCD.

It is worth mentioning that the particular finding of patterns of (HA) and (SD) in an Egyptian sample of OCD patients are in complete accord with the findings of Bejerot et al., 1998b in a Swedish population, and with those of Lyoo et al., 2001 in Korean people and the Cruz-Fuents and coworkers, 2004 results for a Latin American population. These findings might support that the patterns of temperament and character for OCD subjects are quite similar across different cultures and ethnicities.

Impact of Self-esteem on OCD:

Correlational analyses indicate that low self-esteem is significantly correlated to higher total Y-BOCS severity as well as to higher obsessions severity with no relation to compulsions severity. Comparative study between mean self-esteem scores of patients with continuous and progressive course (poor prognosis) and patients with episodic and improving course (good prognosis) of OCD subjects revealed that the former group of patients had significantly lower self-esteem scoring than the latter group. Non compliant OCD patients on treatment had significantly lower self-esteem than compliant patients. Lower self-esteem also was significantly correlated to poorer functioning and worse QoL. Low self-esteem was correlated to the overall duration of illness, and time delay for seeking treatment of OCD.

The cognitive disturbance found in OCD patients may explain this. OCD subjects always place greater emphasis on relationships or the opinion of others. They also reported fears that others would see them in a completely negative manner, suggesting sensitivity to blame and criticism which lower the self-esteem scores in patients with greater obsessional severity. This finding is also consistent with the notion that generalized low self-esteem may occur as a consequence of having an OCD, or as an aspect of that specific disorder, or possibly as a general vulnerability factor as stated by Fennell in 1997.

Impact of Locus of Control on OCD:

Higher locus of control scoring (more towards external locus of control) was significantly correlated to higher Y-BOCS

severity and higher compulsions severity. There was no correlation between locus of control and obsessions severity. Comparative study between mean locus of control scores of patients with continuous and progressive course (poor prognosis) and patients with episodic and improving course (good prognosis) of OCD subjects revealed that the former group of patients had significantly higher (external) locus of control scoring than the latter group. Non-compliant OCD patients had significantly higher (external) locus of control scoring than compliant patients. Higher (external) locus of control also was significantly correlated to poorer functioning and worse QoL.

The significant positive association between the higher locus of control scoring and the compulsion severity may be explained partly by the fact that subjects with external locus of control have a tendency to blame others for their actions, and in turn, others should take control for their actions. This would reduce their initiation to resist or to change particular acts (compulsions) which may give a greater compulsion severity in those with more external pattern of locus of control.

In contrast to our findings McWilliams et al. (2006) found that those with high external locus of control typically believe that experts, such as mental health care providers, had a great deal of influence and as such would be likely to cope with psychiatric disorder by seeking the assistance of such individuals. This finding could also indicate that seeking treatment from others is generally perceived as a passive coping method that relies on the efforts of others.

The limitations of this study need to be acknowledged: 1) The current results could not be easily generalized to individuals with OCD in the community, since the OCD subjects in this study were mostly recruited from the psychiatric outpatient clinic; 2) The fact that OCD is known to be a heterogeneous disorder with several hypothesized subtypes. Because of the relatively small sample of the study, this may limit the generalization of these findings. So, the results can be regarded only as suggestive; 3) No follow-up data have been presented; and 4) Personality features might not be accurately elicited in part because their assessment might have been influenced by their current axis I current symptoms. Moreover, informants were not available for many cases to be questioned in order to get more accurate personality profiles.

Despite the limitations of the current study, yet this is the first report of its kind for Egyptian patients with OCD. The information of the current study may enable the therapeutic team to subgroup OCD subjects, according to their personality profile, and possibly contribute to developing a more effective and specific treatment strategy for every OCD-personality subtype. It is important to examine personality not only on a scale-by-scale basis, but rather within the context of an overall profile. Understanding the impact of personality components on the OCD patients' quality of life may allow the design of more broadly effective clinical interventions and a more judicious allocation of treatment resources.

Conducting the same study but on a longitudinal basis studying patients at baseline and follow them up after a certain period while they are taking a fixed dose of a certain well-studied pharmacological

treatment for OCD to evaluate the impact of the same personality profile on treatment outcome. This can be done using behavioral therapy or using combined therapies. It also should be replicated to demonstrate the impact of personality profile on all other axis I disorders.

The term "personality disorder" is used in such a disparaging manner in many clinical practices that labeling a patient with an axis II diagnosis is tantamount to calling the patient irreparable. Yet, personality disorders may be the most important variable in predicting outcome (Shea et al., 1990). The biological underpinnings suggest that many of these behaviors are not learned but preordained. The vast number of afflicted individuals with personality disorders – who are in psychiatric hospitals or in jails or simply with worse clinical picture and quality of life of their illnesses – indicates a need to find ways to help these individuals. The aforementioned studies in addition to this one provide a starting point for treating these individuals and for future research efforts. Successful work in this area will reduce what is currently an economic burden on society and a terrible illness for those afflicted patients.

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Authors:

Kamel M
Emeritus Professor in Psychiatry
Institute of Psychiatry
Faculty of Medicine
Ain Shams University

Asaad T
Professor in Psychiatry
Institute of Psychiatry
Faculty of Medicine
Ain Shams University

Haroun El Rasheed A
Assistant Professor in Psychiatry
Institute of Psychiatry
Faculty of Medicine
Ain Shams University

Shaker N
Lecturer of Psychiatry
Institute of Psychiatry
Faculty of Medicine
Ain Shams University

Abulmagd M
Speacilst in Psychiatry
El Nile Sanatorium

Address of Correspondence

Haroun El Rasheed A
Assistant Professor in Psychiatry
Institute of Psychiatry
Faculty of Medicine
Ain Shams University

email: amanyhelrasheed@yahoo.com

Mood Disorder: Comparative Study between Old and Young Age Depressed Patients

Eissa A, Elsaeed H., Sabri R. and Elshahawi H.

Abstract

Depression and cognitive impairment are among the most important mental health problems and have sever consequences. Investigations of cognitive disturbances among patients with mood disorders have yielded inconsistent results. Although marked neuropsychological deficits have been reported in elderly patients and in young age patients with severe depression, the severity of cognitive impairments in medically healthy younger ambulatory adults with depression has not been well characterized. This study aimed at comparison of sociodemographic background, depression severity, and cognitive deterioration pattern in elderly depressed with young depressed patients. Sixty cases of both sexes ,half of them above age of fifty, cases were selected from out patient clinics of the institute of psychiatry and geriatrics clinic, Ain shams university, each case subjected to history taking using Ain shams psychiatry interview sheet, physical examination, and psychiatric examination. Diagnosis of depression according to ICD-10 criteria and Hamilton rating scale for severity of depression. Also ICD-10 check list for mental disorders, A comprehensive battery of standard neuropsychological tests for measuring of cognitive functioning including subsets of Wechsler memory scale - revised WMS-R test, and Vigil continuous performance test were administrated. A comparable control groups consisted of sixty volunteers apparently healthy of both sexes, half of them below age of fifty and each subject underwent the same as cases. The study results showed a significant difference between depressed elderly and depressed young patients in some cognitive functions for memory and attention, also in some sociodemographic data, and in severity of depression also there was a highly significant statistical difference as regards age and age of onset of the illness. These findings means that the change in cognitive profile in both patients group is not due to duration of illness it self but due to age and age of onset of depression. The study recommends consideration of cognitive affection in rehabilitation plan, and further studies to ensure our results.

Introduction

Depression and cognitive impairment are among the most important mental health problems in elderly people. Depression, sub-threshold (for DSM-IV diagnosis of major depression) depressive symptoms and cognitive impairment have severe consequences, including diminished quality of life, functional decline, increased use of services, and high mortality ***(Alexopoulos GS, et al., 1996, Unützer J, et al., 2000, Diana D, et al., 2005)***. Late onset depression and cognitive impairment often occur together, suggesting a close association between them ***(Migliorelli R, et al., 1995, Jorm AF, 2001, Zubenko GS, et al., 2003)***. It is not known, however, whether depression leads to cognitive decline or vice versa ***(Jorm AF, 2001, Schweitzer I et al., 2002)***. Clinical practice and research evidence suggest that depression precedes cognitive decline in old age ***(Devanand DP et al., 1996, Yaffe K et al., 1999, Schweitzer I, et al., 2002, Paterniti S et al., 2002, Green RC et al.,***

2003, Wilson RS et al., 2004). Late-life depression has also been associated with other adverse outcomes, such as increased medical morbidity ***(Murphy E, 1983, Baldwin RC, 1991, Alexopoulos GS 1995),*** increased use of health services ***(Unützer J, et al, 1997)*** and, in some studies, mortality ***(Penninx BW, et al., 1999, Covinsky KE, et al., 1998, Pulska T, et al., 1997, Whooley MA, Browner WS, 1998)***. According to the Global Burden of Disease Study, major depression ranks fourth in the world among causes of early death and disability ***(Murray CJL and Lopez AD, 1997)*** and research findings about the association between depression and mortality have been contradictory ***(Pulska T, et al., 1997, Whooley MA and Browner WS, 1998, Schulz R, et al., 2000, Wulsin LR, 2000)***. A Number of research teams have reported statistically significant associations between depressive symptoms and mortality. Some of these studies have not been able to control for differences in a number of demographic, medical, and behavioral health risk factors that may be associated with both depression and the risk of death and thus might confound this relationship. However, Schulz et al. 2000 and Covinsky et al. 1998 found a statistically significant relationship between increased depressive symptoms and mortality after adjustment for comorbidity, functional impairment, and cognitive impairment. A subset of studies has focused on the relationship of depression and cardiovascular mortality or the relationship between depression and mortality in patients with cardiovascular disease. These studies have reported significant associations between depression and mortality ***(Barefoot JC, et al., 1996, Barefoot JC and Schroll M, 1996, Murberg TA, et al., 1999, Frasure-Smith N, et al., 1999, Frasure-Smith N, et.al., 1993, Kaufmann MW, et al., 1999)***.

Objectives

1. Study the effect of age on the depressive of the old age.
2. Describe the pattern of cognitive affection of elderly depressed patients and comparing it by that of younger depressed patients.
3. Study if there is different in confounding variables, remission rates of depression in patients in late life from those in midlife.

Subjects and Method

Site of the study

The cases were selected from the institute of psychiatry, Ain Shams University Hospitals.

Selection of Subjects

Patient group:

They consisted of 60 patients suffering from unipolar depression according to the diagnostic criteria for research of the ICD-10, the sample was divided in to two equal groups one group below the age of 50 years and the other above 50 years all of them were tested at the acute state before starting treatment.

Inclusion criteria

Patients presenting with symptoms fulfilling the criteria for the diagnosis of depression according to the ICD-10 Diagnostic Criteria for Research.

Exclusion criteria

- Patients with below average intelligence.
- -Patients having organic illness, other psychiatric illness, or history of neurological, or drug abuse disorder or due to their refusal to enter the study.

Control group

The control group consisted of 30 individuals above the age of 50Y and 30 of them below this age with no apparent physical or psychiatric morbidity. They were matched for age, sex, and other demographic variables as far as possible with the patient group. They have no family history of any psychiatric disorder**.**

Methods

Study proper

The study proper was conducted in the period from February 2005 to the August 2005. The patients were subjected to full history using Ain Shams psychiatric interview sheet with stress on history suggestive of previous depressive symptoms, Patients were diagnosed according to the research and diagnostic criteria of the international statistical classification of diseases and related health problems (ICD-10) and the ICD-10 (1994) symptom checklist for mental disorders.

All patients underwent the following tests; (1) Wechsler memory scale revised, (2) Vigil continuous performance test, (3) Hamilton rating scale for severity of depression.

Informed Consent was taken from all subjects before they were allowed to enter the study

The control group underwent the same tests in addition to General health questionnaire.

Tools

1. Hamilton depression rating scale (HDRS)

It is a standardized measure of the phenomenology of a depressive syndrome. The total score on 17 item ranging from 0-50, scores of 7 or less considered normal; from 8-13 is considered mild; 14-18 is moderate; 19-22 is severe; and 23 and above is considered very severe.

2. General Health Questionnaire (Arabic version)

It is a self-administered questionnaire for the detection of mental disorders. There are 4 forms of GHQ: the original 60 items, and 3 shorter versions with 30, 28, 12 items. The scale of 28 items was used in its Arabic version ***(Okasha et al., 1988)***.

3. Neuropsychological Assessment:

The following tests are used for assessment of major areas of cognition:

a. Subtest of Memory (Wechsler Memory Scale Revised) ***(Wechsler, 1987)***.
   This battery is composed of a variety of subtests measuring free recall or recognition of verbal and visuospatial material, measures of recall of personal information, attention and concentration. Four of the eight subtests of the WMS-R that present good assessment of memory were chosen to the present study, they are as follows:
   I- Verbal Paired Associates: immediate and delayed recall
   II- Visual Paired Associates: immediate and delayed recall
b. Continuous Performance Test:
   Continuous performance test is used to measure reaction time, attention, vigilance, and sustained attention. Diminished sensitivity is a sign of decreased vigilance and results in a high miss rate (errors of omission). The response criterion can be diminished leading to a high false positive rate (errors of commission). Reaction time is variable that represents the average time from the onset of each stimulus to the initiation of each response.

Statistical methods

SPSS statistical software package was used for data analysis (Version 13.1, 2003, Echosoft Corp., USA). Data were expressed as mean±SD for non-numerical or

quantitative data, while as % for numerical or categorized data. The following tests were used:

1. Wilcoxon Rank Sum test for comparison between two groups for non-parametric data.
2. Chi-square test for comparison between 2 independent groups as regards proportions or percentage for numerical data.
3. Ranked Sperman correlation test to evaluate the possible association between each 2 variables among the studied group.
4. The probability of error (p) value was used to indicate level of significance as follows:

P>0.05: non significant, P<0.05: significant,
P<0.01: highly significant, P<0.001: very highly significant,

Results

Comparing depressed elderly >50ys old (group I) with depressed younger <50ys old (group II) as regards age, age of onset of depression, and duration of illness, results were as follow:

- For group I mean age ± SD was 60.90 ± 6.45ys while that for group II was 31.16 ±7.8. There was a highly sig. Stat. Diff. Between the two groups (P value < 0.01).
- For group I mean age of onset ± SD was 54.03 ±10.86ys, and that for group II was 26.3±8.04ys, and there was a highly sign. Stat. Diff. Between the two groups (P value < 0.01).
- For group I mean duration of illness ± SD was 6.94±7.4 while that for group II was 4.87±4.42ys and there was a non sign. Stat. Diff. which means that the change in cognitive profile is due to age and age of onset of depression and not to the duration of illness itself.
- Sex distribution in group I patients were 3 males (10%), 27 females (90%) while group II were 7 males (23.33%), 23 females (76.67%), there was no statistical significant difference between the two groups (P value > 0.05). meanwhile the majority of cases were females in concordance with sex distribution of depression (more in females).
- Marital distribution in group I patients was 18 (60%) were single & 12 (40%) were married, while group II were 12 (40%) single & 18 (60%) were married with no statistical significant difference (value > 0.05)
- Regarding number of episodes there was no statistical significant difference between the two groups.

Table (1): Distribution of patients according to level of education

Education	illiterate	Read & write	primary	secondary	university	P value
Group I	15 (50%)	12 (40%)	3 (10%)	0	0	< 0.001
Group II	2 (6.67%)	9 (30%)	3 (10%)	9 (30%)	7 (23.33%)	

Regarding level of education there was highly significant statistical difference between the two groups (50% of old aged depressed patients were illiterate).

Table (2): Distribution of patients regarding severity of depression

Severity	Severe	Moderate	P value
Group I	14 (46.67%)	16 (53.33%)	< 0.001
Group II	27(90%)	3(10%)	

Regarding severity of depression there was highly significant statistical difference between the two groups (90%) of old aged depressed patients were diagnosed as severe depression).

1- Comparing depressed cases > 50 ys old with their control > 50ys old we found a high statistical significant difference between the two groups as regards visual I and verbal I for regist. and verbal I for recall.

Table (3):

	Registration				**Recall**			
	Visual I		**Verbal I**		**Visual I**		**Verbal I**	
	mean	**SD±**	**mean**	**SD±**	**mean**	**SD±**	**mean**	**SD±**
Group I	8.06	3.89	13.76	4.81	3.30	1.96	5.23	1.90
Control I	10.40	2.09	18	1.57	4	1.11	6.8	0.76
P value	<0.001		<0.001		>0.01		<0.001	
Signi.	H.sig		H.sig		Non.sig		H.sig	

2- Comparing depressed subjects <50ys old with their control <50ys old we found a highly sign. stist. diff. Between cases and control as regards visual I, verbal I for registr. and verbal I for recall but visual I for recall has only a sign. St.diff.

Table (4):

	Registration				**Recall**			
	Visual I		**Verbal I**		**Visual I**		**Verbal I**	
	mean	**SD±**	**mean**	**SD±**	**mean**	**SD±**	**mean**	**SD±**
Group II	10.8	3.9	16.26	2.97	4.13	1.5	5.86	1.25
Control II	14	2.33	19.36	2.49	5	0.98	7.03	1.09
P value	<0.001		<0.001		<0.01		<0.001	
Signi.	H.sig		H.sig		Sig		H.sig	

3- Comparing depressed case>50ys with depressed case <50ys we found a highly stat. Sign diff. between the two groups in visual I and only a sign. St. diff. In verbal I for regist.

Table (5):

	Registration				Recall			
	Visual I		Verbal I		Visual I		Verbal I	
	mean	SD±	mean	SD±	mean	SD±	mean	SD±
Group I	8.06	3.89	13.76	4.81	3.30	1.96	5.23	1.90
Group II	10.8	3.9	16.26	2.97	4.13	1.5	5.86	1.25
P value	<0.001		<0.01		>0.01		>0.01	
Signi.	H.sig		Sig		Non.sig		Non.sig	

4- Comparing the two control groups we found a highly sig. st.diff .between the two groups in regist, tests and in visual I for recall.

Table (6):

	Registration				Recall			
	Visual I		Verbal I		Visual I		Verbal I	
	mean	SD±	mean	SD±	mean	SD±	mean	SD±
Control I	10.40	2.09	18	1.57	4	1.11	6.8	0.76
Control II	14	2.33	19.36	2.49	5	0.98	7.03	1.09
P value	<0.001		<0.01		<0.001		>0.01	
Signi.	H.sig		H.sig		H.sig		Non.sig	

In this study we select vigil continous performance test which test attention and comparing different groups and results were as follow:

1- In comparing depressed elderly >50ys old and their control >50ys old volunteers there was H.sig. Statis.difference between the two groups for total omission and a very highly stat. sign.diff. for total commission .

Table (7):

	Total omission		Total commission		Average delay	
	mean	SD±	mean	SD±	mean	SD±
Group I	15.23	13.77	23.23	18.81	523.16	72.52
Control I	12.40	18.25	8.80	6.04	503.11	32.43
P value	<0.01		<0.001		>0.01	
Sig	H.Sig		V.H.sig		Non sig	

2- In comparing depressed subjects <50ys old and their control there was a sign. st. diff. between the two groups for total omission and average delay and a highly sign. diff for total commission.

Table (8):

	Total omission		Total commission		Average delay	
	mean	**SD±**	**mean**	**SD±**	**mean**	**SD±**
Group II	11.33	10.50	11.70	10.08	516.31	62.75
Control II	2.76	1.92	3.26	2.66	502.98	39.28
P value	<0.01		<0.001		0.01	
Sig	Sig		H. sig.		Sig.	

3- In comparing depressed elderly >50ys and depressed younger <50ys their was a highly sign. st. diff. for total commission.

Table (9):

	Total omission		Total commission		Average delay	
	mean	**SD±**	**mean**	**SD±**	**mean**	**SD±**
Group I	15.23	13.77	23.23	18.81	523.16	72.52
Group II	11.33	10.50	11.70	10.08	516.31	62.75
P value	>0.01		<0.01		>0.01	
Sig	Non. Sig.		H. sig.		Non sig	

4- In comparing non depressed elderly control (>50ys) and non depressed younger control (<50ys), there were a hihly significant sta. diff. For total omission and average delay and a very highly sig. diff. for total commission.

Table (10):

	Total omission		Total commission		Average delay	
	mean	**SD±**	**mean**	**SD±**	**mean**	**SD±**
Control I	12.40	18.25	8.80	6.04	503.11	32.43
Control II	2.76	1.92	3.26	2.66	502.98	39.28
P value	<0.01		<0.001		< 0.01	
Sig	H.Sig		V.H. sig.		H.Sig.	

Discussion and Conclusion:

Depressive symptoms were associated with increased risk of mild cognitive impairment (MCI) as ***Deborah E, et al., 2006*** studied in a Prospective, population-based, longitudinal study on a random sample of 2220 adults 65 years or older recruited from 4 US communities. Depression was associated with worse performance in some but not all baseline cognitive composites in a study of ***Ganguli, et al (2006)***, in a twelve-year prospective epidemiological study to examine the relationship between depressive symptoms and subsequent cognitive decline in a cohort of nondemented older adults. Different researchers attempted to study associations between different cognitive functions and depression. Executive dysfunction is often part of the clinical presentation of late-life depression. Impaired ability to plan, organize, initiate, and sequence behavior has been observed in depressed elderly patients ***(Beats BC, et al., 1996 and Nebes RD, et al., 2000)***. ***Christopher F, and***

George S (2004) studied the Longitudinal Association of Initiation/Perseveration and Severity of Geriatric Depression , subjects were 157 consecutively recruited elderly patients (64 men, 93 women; mean age 72 years; standard deviation (SD): 6.9) enrolled in a longitudinal study of the course of geriatric depression. Patients were included if they were 60 years old or older, met Research Diagnostic Criteria (RDC) and DSM-IV criteria for unipolar major depression and had a score of 18 or higher on the 24-item Hamilton Depression Rating Scale (Ham) IP was assessed with the DRS-IP. The DRS-IP domain assesses verbal initiation and verbal, motor, and graph motor perseveration and results showed a significant association between concurrent Ham-D and DRS IP scores p value <0.0001, suggesting an association between IP and depression severity. Also Michael A, et al., 2005 studied Neuropsychological Differences between Late-Onset and Recurrent Geriatric Major Depression using neuropsychological measures of executive functioning and episodic memory, as well as psychopathological symptoms and comorbid medical illness, were examined in a total of 116 older adults. They found Patients with late-onset major depressive disorder showed specific deficits in attention and executive function, whereas patients with recurrent major depressive disorder exhibited deficits in episodic memory.

We studied the pattern of cognitive affection by age in elderly by comparing cognitive functions in control I (> 50ys healthy volunteers) with that of control II (<50 ys healthy volunteers) and we found a highly statistically significant difference between them in registration tests and visual I for recall but no significant statistical difference as regards verbal for recall. So, age has no effect on verbal paired associate for recall but has a highly statistically significant effect on registration and visual recall. Also, age has a highly statistically significant effect on total commission and only a significant effect on total omission and average delay for vigil continuous performance test so, registration, recall, and attention of elderly is affected by age significantly. Also our study demonstrated a negative correlations between age of persons and recall in non depressed elderly and registration in non depressed younger persons and this findings means that as the person gets older his registration and recall of memory decreases. And as regards vigilance tests as the persons ages average delay gets longer among young controls and total omission decreases in older controls and this means that as the age increases the attention and vigilance decrease. While for effect of depression on cognitive functions in elderly > 50 years old we compare them with their control group and we found a highly significant statistical effect on registration tests of memory and a verbal recall while visual recall is not stat. Significantly affected and this means that depression in elderly worsen registration which is already affected by age while a visual recall is not statistically sig. worsened by depression but depression is associated by impact in verbal recall which is not found to be affected sign. by age, in comparison to a study done by ***David J, et al., 2004*** on 500 subjects 85years old at least , to study Temporal relation between depression and cognitive impairment in old age they found immediate recall, and delayed recall to be affected. Also *Michael A, et al., 2005,* found episodic memory to be affected in elderly depressed patient with recurrent major depression.

Kathryn A, et al., 2000 studied subtypes of cognitive impairment in depressed older adults, and he found the largest subgroup had memory impairment, whereas two smaller subgroups had executive or attention deficits in addition to memory impairment, this finding is consistent with observations of others who have reported memory, executive, and attention deficits in some depressed elderly patients ***(Boone K et al., 1994, Kinderman S, and Brown G, 1997)***. For effect of depression in elderly on attention there was a statistical significant effect on total omission and a highly st. sign. effect on total commission and a non statistical significant effect on average delay and this can be explained by worsening of attention with depression total commission more than total omission but average delay not sign. affected due to depression in elderly, Affection of attention in elderly depressed also found in ***David J, et al., 2004*** study. We studied the effect of depression on cognitive functions in young (< 50 years old) by comparing young depressed group with their control and we found a highly significant effect on registration tests and verbal recall and this is as in elderly, but a statistically significant effect on visual recall which is not affected by depression in elderly under the study. Also we found depression to affect attention and vigilance tests with a highly statistically significant on total commission as we found in elderly and only a significant effect on total omission and average delay which differ from effect of depression on elderly in average delay this finding is consistent with observations of others studies as in ***King DA, et al., 1991, Raskin A, 1986, and Emery O, 1988.***

We compared elderly depressed with those younger depressed as regards cognitive functions affection associated with depression and we found for registration a highly statistically significant difference in visual paired associate and only a significant difference for verbal paired associate test while there was a non significant statistical difference for recall tests. This means that depression in elderly is associated with significant affection of registration but not recall than younger depression. Also elderly depressed showed a highly significant statistically difference as regards total commission test for attention but no significant difference for total omission and average delay tests for attention. This means that attention of elderly depressed is affected in total commission than in younger depressed but no significant difference of attention affection in average delay and total omission than younger depressed. Also we compared elderly depressed under the study with those younger as regards age, age of onset of depression and duration of illness, and we found no significant statistical difference between the two groups as regards duration of illness but a highly significant statistical difference as regards age and age of onset. This means that the change in cognitive profile is not due to duration of illness it self but due to age and age of onset of depression ***also these were found in the studies done by Alex J., and Hari Subramaniam, 2005***. Also there was no statistically significant difference between the two groups regarding sex distribution, marital state, and number of episodes. There were a highly significant statistical difference as regards severity of illness and level of education. Also our study founds a positive correlation between registration and recall of memory in all studied groups. So, impaired either of them indicates impairment of the other and so

impairment of either of them mandate assessment of the other.

Clinical applications

For study of prognosis of depression in old age compared to middle age they found that with control for confounding variables, remission rates of depression in patients in late life are little different from those in midlife, but relapse rates appear higher. These findings underline the importance of assessing factors related to patient age and not just to age itself in evaluations of risk factors for poor prognosis. So, depression is a rich field for research for clinical applications and we thought in our study to describe pattern of cognitive affection of elderly depressed patients and comparing it by that of younger depressed patients.

Recommendation

Identification of pattern of cognitive affection in depressed patients may have implications for clinical research and practice.
Our study results ensure presence of cognitive affection in depression and hence suggest a focused rehabilitation treatment.

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Authors

Eissa A.
Lecturer of psychiatry
Institute of psychiatry
Ain Shams University.

Elsaeed H.
Lecturer of psychiatry
Faculty of medicine
Bani -Sweef University.

Sabry R.
Lecturer of Geriatric Medicine
Ain Shams University.

Elshahawi H.
Lecturer of psychiatry
Institute of psychiatry
Ain Shams University.

Address of Correspondence

Eissa A.
Lecturer of psychiatry,
Institute of psychiatry
Ain Shams University.
E-mail: dr_abeer_eissa@yahoo.com

Impact of stressful job on Quality of life and life satisfaction among doctors: comparative study between oncology and academic doctors

Abdel Razek G, Mahmoud A, El-Saeed H, Hamed H

Abstract

Medical professionals in general and practitioners of oncology specifically face a host of highly stressful issues on a daily basis during the routine practice of their profession. Such stresses include dealing with extremely, and often terminally, ill patients who require and deserve a great deal of emotional support as well as high quality and optimal medical care. The end result of these stresses is reflected in high rates of burnout among medical practitioners. These may affect personal, social and occupational life so our aim to investigate the hypothesis that stressful job could affect quality of life and life satisfaction of oncology doctors, even their method of coping with stress may also affected**.** 45 oncology doctors who agree to share in the study were compared to 45 academic doctors regarding Dealing with Stressful Life Events Scale (D.S.L.E.S.), Quality of Life Scale (Q.L.S.) and Life Satisfaction Scale (L.S.S.). There were high statistical significant differences between both groups regarding the three variables as oncology doctors use negative approaches of coping style rather than positive one and less life satisfaction than academic doctor. Also academic doctor has better quality of life than oncology doctors. Our findings support the concern that medical oncology personnel are experiencing high levels of stress which affect quality of life and life satisfaction so early training of young residents for positive approaches of coping style may improve quality of care for patients and prevent burn out among oncologist.

Introduction

The effective functioning of any health service requires that its staff are maintained in good health themselves. It is clear that health professionals have an increased incidence of psychological morbidity, and there is anecdotal evidence suggesting that this affects their clinical practice. The mental health of staff and patients alike is affected by antecedent life experiences and contemporary work pressures ***(Richard, 2003)*****.** In general, health professionals have increased psychiatric morbidity, with high rates of anxiety, depression, suicide, alcohol and drug misuse ***(Payne & Firth-Cozens, 1987; Heim, 1991; Guthrie & Black, 1997)***. National Health Service (NHS) staff have higher rates of sickness absence than comparable staff groups in other sectors, and levels of staff turnover and wastage are very high. A study of 11 600 NHS staff ***(Borrill et al., 1996; Wall et al., 1997)*** found an overall prevalence of psychological morbidity of 27%, compared with 18% in working people outside the NHS and 30% in the unemployed population. Female doctors and managers were found to be particularly at risk. Many types of clinical work are inherently stressful ***(Payne & Firth-Cozens, 1987)***. Areas where there is a high level of trauma or mortality (accident units, intensive care units, neonatal units) are perhaps the most obvious, but practitioners in all fields have to cope with heavy clinical workloads and ever-increasing administrative demands.

Concern has been expressed about the increase of threats and violence from patients and relatives. Many factors may result in what is called burnout syndrome which describes the end result of stress in the professional life of a physician or caregiver and combines emotional exhaustion, depersonalization and low personal accomplishment. Burnout is particularly relevant in oncology where staff work closely with patients who have life-threatening illnesses and therapy often has only a limited impact ***(Eva et al., 2000)***. Medical oncology personnel considered one of the most stressful medical specialty, so there are many anecdotal reports of burnout, decreased morale, high levels of stress and staff leaving or decreasing their work hours ***(Barni et al., 1996)***. In the study of Carmen et al 2003 Seven thousand seven hundred fifteen oncology physicians were queried by e-mail or during attendance at oncologic meetings and asked to complete a 22-question survey concerning their feelings of personal burnout and their perceptions of physician burnout in the oncology community. Overall, 61.7% of the respondents reported feelings of burnout, with the top three signs being frustration (78%), emotional exhaustion (69%), and lack of satisfaction with their work (50%). The highest-ranked causes for their feelings of burnout included overwork, lack of time away from the office, and reimbursement concerns. As there is few number of researches that systematically determined whether job stresses affect the way of coping, quality of life and life satisfaction of doctors or not, so in our study we investigate the hypothesis that stressful job could affect quality of life and life satisfaction of oncology doctors, even their method of coping with stress may also affected

Objectives

1. Determining way of coping style among oncology doctor versus Academic doctor.
2. To know the relation between type of coping style, quality of life and life satisfaction of oncology doctor.
3. Comparison between oncology doctors and Academic doctor regarding Quality of life and life satisfaction.

Subjects and methods

Our sample taken From department of radiotherapy at Ain Shams University hospital together with various academic department of faculty of medicine- Ain Shams University hospital. Oral informed consent obtained from 45 oncology doctor who agree to share in the study, they compared with 45 academic doctors.

Tools

1. Oral informed consent.
2. Dealing with Stressful Life Events Scale (D.S.L.E.S.): This Scale can measure different methods of dealing with stressful life events and consisted of 30 items, grouped into 3 groups. The first group is positive approach and consisted of 13 items, the second is negative approach and consisted of 7 items and the third is adaptational behaviors and consisted of 10 items ***(Ali, 2003)***.
3. PCASEE Quality of Life Scale: were applied at time of research this scale consisted of 6 subscales which measure different aspect of quality of life regarding physical, cognitive, affective, social, and economic and ego problems ***(Beck et al., 1993)***.

4. Life Satisfaction Scale (L.S.S.): This Scale is consisted of 30 items, and can measure degree of life satisfaction ***(Dessoki, 1998)***.

Statistical analysis:

SPSS statistical software package was used for data analysis (Version 13.1, 2003, Echosoft Corp., USA). Data were expressed as mean±SD for non-numerical or quantitative data, while as % for numerical or categorized data. The following tests were used:

1. Wilcoxon Rank Sum test for comparison between two groups for non-parametric data.
2. Chi-square test for comparison between 2 independent groups as regards proportions or percentage for numerical data.
3. Ranked Sperman correlation test to evaluate the possible association between each 2 variables among the studied group.
4. (only for the last paper) Kruskall Wallis test for discriminating between more than 2 patient groups for non-parametric data.

The probability of error (p) at 0.05 was considered significant, while at 0.01 and 0.001 were highly significant.

Correlation between parameter: critical value (1- tall =0.249, 2- tall=0.294).

Procedures

An oral informed consent obtained from oncology doctors and academic one then D.S.L.E.S, L.S.S. and Q.L.S were performed to both group then statistical analysis done.

Results

Socio-demographic data

Table (1): Age difference among both groups

	Oncologist		**Academic doctors**	
	Mean	**Std. Dev.**	**Mean**	**Std. Dev.**
Age	34.47	4.78	36.73	5.31

The mean age among oncology doctors was 34.47 with standard deviation ±4.78 while, among the academic doctors the mean was 36.73 ± 5.31. With no statistical significant difference between them as shown in **table (1)**.

Table (2): Gender and Marital status difference among both groups:

	Oncologist (%)	**Academic doctors (%)**
Gender		
Males	46.67%	37.78
Females	59.33%	62.22%
Marital status		
Married	75.56%	80%
Not married	24.44%	20%

- 59.33% of the oncologist were females while, among the other group the percent was 62.22. with no statistical significant difference between them
- 75.56% of the oncologists were married while; among the other group the percent was 80%. with no statistical significant difference between them as shown in **table (2)**

Table (3): Comparison between oncologist and academic doctors regarding Quality of life Scale (Q.L.S.)

	Oncologist			Academic doctors			P-value
	Mean	Std. Dev.	Total	Mean	Std. Dev.	Total	
Physical Problems	56.27	11.55	45	74.84	10.22	45	**<0.001** H.S.**
Cognitive Problems	58.44	18.80	45	81.07	12.60	45	**<0.001** H.S.**
Affective Problem	54.67	21.11	45	79.67	11.65	45	**<0.001** H.S.**
Social Problem	60.36	18.64	45	84.89	11.53	45	**<0.001** H.S.**
Economic Problem	52.53	19.23	45	81.51	8.83	45	**<0.001** H.S.**
Ego Problem	58.58	16.45	45	80.26	8.54	45	**<0.001** H.S.**

There was highly statistical significant difference between the two groups regarding Subscales of Quality of Life Scale P= <0.001** H.S. This means that academic doctors showed better quality of life (including physical, cognitive, affective, social, economic, and ego problems) than oncology doctors.

Table (4): Comparison between both groups regarding dealing with stressful life events scale (D.S.L.E.S.)

	Oncologist			*Academic doctors*			P-value
	Mean	Std. Dev.	Total	Mean	Std. Dev.	Total	
Positive Approach	26.98	2.82	45	31.07	2.12	45	**<0.001** H.S.**
Negative Approach	16.89	2.48	45	14.11	2.89	45	**<0.001** H.S.**
Adaptational behaviors	22.2	2.33	45	25.89	2.25	45	**<0.001** H.S.**
Total Scale	66.2	3.57	45	70.91	2.75	45	**<0.001** H.S.**

There was highly statistical significant difference between the two groups regarding Dealing with stressful Life Event Scale P= <0.001** H.S. As academic doctors utilize positive and

adaptational approach more than negative one. Although oncology doctors use negative and adaptational approaches more.

Table (5): Comparison between both group regarding life satisfaction scale (L.S.S.)

	Oncologist			*Academic doctors*			P-value
	Mean	**Std. Dev.**	**Total**	**Mean**	**Std. Dev.**	**Total**	
L.S.S	67.69	13.79	45	91.91	11.12	45	**<0.001** H.S.**

There was highly statistical significant difference between the two groups regarding Life Satisfaction Scale P= <0.001** H.S. This means that academic doctors showed higher life satisfaction than oncology doctors.

Discussion

In our study although both academic and oncology doctors are exposed to stress like other health professional as evidenced by Payne & Firth-Cozens (1987) but the way of coping with such stress is different as academic doctors utilize healthy coping strategy that is to say positive one more than oncologist who utilize mainly negative and adaptational approach. As coping style is one of the most important factors in the development of stress related disorder this may be the reason of high psychiatric morbidity among oncology doctors as shown by Eva et al (2000) who study 681 health professional working in Ontario Oncology Center regarding paychiatric morbidity and burnout syndrome and found that the physician group had the highest prevalence of psychological morbidity and 2 components of burnout. At the same time they compared their findings with those from 2 other studies of physician burnout (as measured by the MBI): one involving Canadian emergency physicians (Lloyd, Streiner and Shannon 1994) and the other medical include oncologists in the United Kingdom ***(Ramirez et al., 1995)***. More physicians in their study than in the other 2 had low levels of personal accomplishment and high levels of emotional exhaustion. On the other hand academic doctors showed better quality of life than oncology doctors. This finding could be expected as life stress and job satisfaction could affect all aspects of quality of life, this was supported also by the findings of *Eva et al 2000* that medical oncology personnel are experiencing burnout and high levels of stress and that large numbers are considering leaving or decreasing their work hours. Similar results regarding life satisfaction scale which show better life satisfaction among academic doctor rather than oncologist, *Wippen et al 1991* found similar results when he make a study over1,000 subscribers of the Journal of Clinical Oncology. About 60% of them were medical oncologists and the rest were radiation or surgical oncologists, he asked them about burn out and impact of job stress on social and personal life, eighty-five percent said that it was affecting their personal and social life. So both social, personal and occupational life are affect each other as in the Mayo Clinic study

2006, who found that As students approached the end of their medical training, they were less likely to be depressed or use excessive alcohol, however, they were more likely to be "burned out". Similar to our study, the study done by Sergant et al 2004 who to determine the quality of life of orthopaedic residents and faculty and to identify the risk factors for decompensation. They identified a large disparity between the two groups, as the resident group reported much greater levels of dysfunction particularly with regard to burnout and psychiatric morbidity.

Conclusion

There are a number of restorative practices were cited. Exercise is well known to reduce stress and relieve depression ***(Mount, 1986)***. *Creagan* highlights the importance for oncologists of involvement in activities distinct from their professional lives and hypothesizes that these individuals make more productive and sympathetic practitioners. Although sabbaticals, vacation and personal time would clearly alleviate burnout ***(Whippen et al., 1991***), other practical changes including flexible schedules, shared positions, on-premise childcare and prioritizing family time may be helpful ***(Lagasse, 2000)***. All these practice aim to reduce job stress and hence improve life satisfaction and quality of life, also early training of medical student and young residents to use positive approach for coping style may has great impact on personal, social and occupational life.

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مقياس مواجهة احداث الحياة اليومية الضاغطه :
Leonard W.poon تعريب على عبد السلام على :
استاذ مساعد علم النفس كلية اداب جامعة الزقازيق فرع بنها ٢٠٠٣ مكتبة النهضه المصريه

مقياس الرضا عن الحياة (Life Satisfaction scale)
تأليف ا.د مجدى محمد الدسوقى استاذ علم الاجتماع جامعة المنوفيه مكتبة النهضة المصريه – مكتبة الانجو المصرية ٢٠٠٢

Authors

Mahmoud A.
Lecturer of psychiatry
Institute of psychiatry,
Ain Shams University.

Abd Elrazek G.
Lecturer of psychiatry
Institute of psychiatry,
Ain Shams University.

Correspondence

Mahmoud A.
Lecturer of psychiatry,
Iinstitute of psychiatry,
Ain Shams University.
E-mail: dr_abeer_eissa@yahoo.com

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Hippocampal volume in chronic schizophrenia and first episode drug-naïve psychotic patients

El Tayebani M., Abdel-Azim Kh. El Gamal M. and Ahmad Kh.

Abstract:

Reduced hippocampal volume is a structural abnormality frequently found in Schizophrenia. The reduction may be a consequence of neurodevelopment events preceding the illness and/or a result of the disease process itself. Our aim is to examine whether hippocampal volume reduction is present early in the disease or it is the effect of chronicity. Magnetic resonance imaging brain scans of patients in their first episode psychosis were compared with those of chronically ill schizophrenic patients. Scans for controls matched to both patient groups were also performed. Symptoms severity was also assessed. We found that both groups of patients had smaller hippocampal volumes compared to controls. The reduction in volume was greater in chronic than in acute young patients. The findings support both hypotheses of developmental and progressive hippocampal reduction in schizophrenia.

Introduction:

Schizophrenia is a disabling illness, but its etiology remains poorly understood ***(Silver and Davis, 2004).*** It remains to be determined whether schizophrenia is neurodegenerative process that beings at about the time of symptom onset and manifests as progressive volumetric loss, or whether it is better characterized as neurodevelopmental process that results in abnormal brain volume beginning at an early age ***(Maynard et al, 2001).***

Neurodevelopmental models postulated an important role for aberrant hippocampal morphology in the patho-physiology of schizophrenia. There is considerable evidence from postmortem (***Arnold et al 1995***; ***Benes et al, 1991; Jeste & Lohr, 1989 Kovelman et al, 1984***) and magnetic resonance imaging (MRI) studies ***(Bogerts et al, 1993; Shenton et al, 1992; Bogerts et al, 1990)*** that patients with schizophrenia have hippocampal structural abnormalities. About 4% reduction in bilateral hippocampal volumes had been identified in patients with schizophrenia relative to controls ***(Nelson et al, 1998).***

In recent years with the advent of brain imaging methods such as MRI, it has become possible to study patients during their first episode of psychosis, before disease effects are obscured by the confounding influences typical of cases of chronic schizophrenia ***(Shenton et al, 2001).*** Studies in first episode psychosis have inconsistently reported brain volume changes in that group of patients, relative to control. While some studies reported smaller hippocampi ***(Gur et al, 2000a)***, others reported no difference in hippocampal volume in first episode patients relative to control (***Chan et al, 2002).***

Hippocampal volume reduction has been reported in unaffected first degree relatives of schizophrenic patients ***(Seidman et al, 2002).*** However, this finding is also inconsistent. More recent studies ***(Velakoulis et al, 2006; McDonald et al, 2006; Schulze et al, 2003)*** revealed no

volume reduction within the ultra high risk group.

The developmental versus neurotoxic hypotheses for schizophrenia were discussed by ***Cotter and Pariante 2002*** who concluded that brain changes founded at psychosis onset or possibly after are not purely developmental and not specific for schizophrenia.

Velakoulis, et al 1999 identified smaller hippocampal volumes bilaterally with chronic schizophrenia and with first-episode patients than control, but also noted its non specificity where it is present within schizophrenic and non schizophrenic affective groups. On the other hand, ***McDonald and colleges 2006,*** reported hippocampal volume reduction only in schizophrenic patients, but not in bipolar disorder patients or in their unaffected relatives.

In contrast, ***Delisi et al 1991*** found no differences in brain volume at illness onset and this occurred with reduction of whole brain volume after 4 years. These reports as well as results of right hippocampal volume reduction association with illness duration may raise neurotoxic hypothesis of schizophrenia ***(Volkoulis, et al 1999).***

This inconsistency in results could be explained by many factors such as technical variability, small sample size, and/or failure to match for age, gender or handedness.

Objectives:

Although many quantitative magnetic resonance imaging studies have found volume reduction in the hippocampi of patients with schizophrenia compared with those of normal control subjects, others have not. Therefore, it remains questionable.

Aim of the Study:

Our aim is to study hippocampal volume in both chronic schizophrenia and first episode drug-naïve psychotic patients. Then, test the illness duration, severity and drug treatment on the brain structural findings.

Methods:

The study had been conducted at the Psychological Medicine Hospital, Kuwait, over 6 month period from the 1st of August 2005 to 31st of January 2006. Written informed consent was a prerequisite for participation. Patients recruited had been divided into two main groups:

- ***Group I (Drug – naïve patients with first episode psychosis):***

A total of 32 drug–naïve patients with first episode psychosis had been recruited from those presented to the out-patient, causality or in-patient facilities of the Psychological Medicine Hospital. Only 25 were enrolled and completed the protocol. Of the 7 patients who were screened but excluded, 4 were non Kuwaiti, 2 were diagnosed as substance induced psychosis, and one refused to give consent.

- ***Group II (Chronic patients with schizophrenia):***

Twenty Five patients with more than 10 years duration of illness constituted the chronic illness group. They were randomly selected from the chronic in-patient wards. Their duration of illness, and type of antipsychotic drug used- whether typical or atypical- were also mentioned.

Clinical Diagnosis and assessment:

Patients meeting the inclusion criteria were interviewed by one of the research psychiatrists. Diagnostic interviews included: Demographic data for all

patients, their medical and/or psychiatric history, family history, and duration of illness. For the 1st episode psychosis patient group, family members & data providers were strictly asked to determine when exactly (to the nearest week) did they notice any change in the patients' behavior. Patients with noticeable symptoms for more than one month were eliminated from the study.

All participants underwent the structural clinical interview for DSM-IV Axis I disorder (SCID; First et al 1995). Patient's symptoms severity was evaluated with the Positive and Negative Syndrome Scale (PANSS; Kay, el al 1987) and the Clinical Global Impression (CGI; Guy, 1976).

Inclusion criteria for patients:

-Drug-naïve patient experiencing their first-episode psychosis (constituting the first group).

Age 16-50 Years.

Only Kuwaitis were included.

Exclusion criteria:

History of prior use of neuroleptics or ECT treatment, organic or substance – induced psychosis, &/or metallic implants or pacemakers.

Control Subjects:

Forty healthy control subjects were recruited from the radiology department at Ibn Sina hospital - by one of the researchers (radiologist) - after completing a semi-structured sheet & the General Health Questionnaire (Goldbarg 1972). Control subjects were divided into two groups. Twenty healthy control subjects matched the acute patients group, and the other 20 matched the chronic group for age, gender, and education. Exclusion criteria were any Axis I DSM-IV psychiatric disorder, history of substance abuse, history of any gross medical or neurological disorders.

Imaging protocol & volume measurements:

The outline of the temporal lobe was traced on each section, and the outlines of the amygdala and hippocampus were traced on the sections in which they appeared. The posterior boundary of the hippocampus and temporal lobe was set at the level of the last section on which the midbrain collicular plate appeared. For the hippocampus, the choroid fissure was the superior boundary, the inferior temporal horn of the lateral ventricle was the lateral boundary, and the white matter of the para-hippocampal gyrus was the inferior boundary. Anteriorly, the white matter of the alveus delineated the boundary between the hippocampus and amygdala. If the delineation between the amygdala and hippocampus was not seen, the tracing followed the lateral and inferior boundaries to the medial edge of the gray matter; a straight horizontal line then was drawn to the beginning of the trace at the lateral edge. The resulting outlined areas were used to calculate the estimated left and right hippocampal volumes.

Magnetic resonance image acquisition & processing:

MR imaging was obtained using single 1.5-T scanner (Signa horizon, General Electric medical system) Head positioning was standardized using cantho-meatal landmarks, head movement was minimized by foam padding and straps across the forehead & chin. An 8 channel high resolution head coil was used. A 3D volumetric spoiled gradient recalled echo in the steady state sequence generated 60 contiguous 3mm coronal oblique slices

perpendicular to hippocampus TR 9, TE 2, ET 0, matrix 320X256, FOV 24cm & Axial T2 FSE TR 7000 TE 88 ET 25 5mm thick with 1.5 spacing matrix 512X256 FOV 24 cm to exclude organic lesions & other pathologies. Magnetic resonance imaging data were transferred to a workstation (Advantage windows V4.1) and analyzed. Hippocampal volumes were estimated using manual tracing & the above mentioned defined anatomical criteria. One rater performed all hippocampal tracing included in the analyses. One limitation of our study in comparison with previously published article discussing the same subject, we don't correlate hippocampal volume with the whole brain volume, yet advantages of our study are thinner slices perpendicular to hippocampus of the 3D volume acquired & more defined anatomical landmarks.

Statistical methodology:

Data were collected and coded then entered into an IBM compatible computer, using the SPSS version 12 for Windows. Entered data were checked for accuracy then for normality, using Kolmogorov-Smirnov test. Qualitative variables were expressed as number and percentage while quantitative variables were expressed as mean ($\overline{X}$) and standard deviation (S.D.). The arithmetic mean ($\overline{X}$) was used as a measure of central tendency, while the standard deviation (S.D.) was used as a measure of dispersion.

The following statistical tests were used:-

Independent samples t-test was used as a parametric test of significance for comparison between two sample means, after performing the Levene's test for equality of variances.

Independent samples Mann-Whitney's U-test (or Z-test) was used as a nonparametric test of significance for comparison between two sample medians.

The χ^2-test (or likelihood ratio =LLR) was used as a non-parametric test of significance for comparison between the distribution of two qualitative variables.

The Kruskal-Wallis test (χ^2-value) was used as a non-parametric test of significance for one-way comparison between more than two samples means, when the one-way ANOVA test was not appropriate.

The Spearman's rank correlation coefficient (r) was used as a non-parametric measure of the mutual relationship between two not-normally distributed quantitative or ordinal variables.

A 5% level is chosen as a level of significance in all statistical significance tests used.

Results:-

Demographic Data and clinical characteristics:

As shown in table (**1**), there was no significant difference between patients and their age, gender, and education- matched healthy control subjects. It also shows that more than half of patients-either acute or chronic were single, while a large proportion of healthy control subjects were married. The differences in the current marital status between all groups were at a significant level (***p=0.002***).

Nine patients with 1st episode psychosis (*36%*) had family history of mental disorders compared to 15 chronic schizophrenics *(60%)*. Statistical difference between both groups was insignificant (χ^2=***2.89*** & ***p*** value=***0.09***). Five *(20%)*; 4 *(16%)*; 3 *(12%)* & 2 *(8%)* of the studied chronic schizophrenics had family history of schizophrenia; more than one disorder;

epilepsy & mental retardation, respectively, compared to 4 *(16%)* of the 1st episode psychosis patients group who had family history of schizophrenia; 2 (*8%*) had family history of more than one disorder & only one patient *(4%)* reported family history of substance abuse.

Regarding current medical condition & current use of medications, 3 *(12%)* of 1st episode psychosis patients & only 1*(5%)* of their control group have diabetes mellitus & were receiving regular medical treatment. While, 16 *(64%)* of the chronic schizophrenics & only 3 *(15%)* of their control group have diabetes mellitus &/or hypertension & were put on regular medications. Comparison between all groups revealed high significant difference (Likelihood Ratio=***56.3*** & ***p*** value=***0.000***).

Table (**2**) summarizes the clinical characteristics of the 1st episode psychosis and chronic schizophrenia patient groups. As shown in the table, although total scores of **PANSS** (Positive & Negative Symptoms Scale) & **CGI** (Clinical Global Impression scale severity) were higher in 1st episode psychosis patients than in chronic schizophrenics, yet, there were no statistical significant differences between both groups. Patients with 1st episode psychosis tended to have higher PANSS negative symptoms scores, while chronic patients had higher PANSS positive scores. The differences did not rise to a statistically significant level.

Hippocampal volume results:

The volumes of the right and left hippocampi in the four studied groups are shown in table (**3**). The major finding from this table is the significant reduction in hippocampal volumes for both patients groups relative to their control groups (***p=0.000***).

The reduction was more in the left hippocampus than in the right hippocampus in both patient groups, even though the difference between left & right hippocampal volumes was not statistically significant in the four studied groups *(**p > 0.05**)*.

Regarding effect of gender on hippocampus volume measures in all of the 4 groups both on the Rt. & Lt sides, all results were insignificant between Rt. & Lt hippocampus after putting the gender effect (using t-test for equality of means) *(p > 0.05),* except for female chronic schizophrenic patients where their mean Lt. hippocampal volumes (*2329.56 mm³ ± 102.89*) was significantly different than their mean Rt. hippocampal volumes (*2030.55 mm³ ± 304.02*), *(t-value = **2.79** & p = **0.02**)*.

To verify the effect of aging on normal hippocampal volume, we correlated the variable of age to the hippocampal volume in both of the control groups with different means of age (*28.3 ± 8.2* years in control group of 1st episode psychosis patients & *44.5 ± 7.8 years* in control group of chronic schizophrenics) by using ***Spearman's rho technique***, we found no significant correlations between age & hippocampal volumes neither on the right nor on the left hippocampi in both control groups *(**p > 0.05**)*.

After neutralizing the effect of age on normal hippocampal volume, we collected both of the control groups in one ***main control group*** *(n = 40)* then by Post Hoc tests (detailed ANOVA test), we could compare means of hippocampal volumes of the remaining three groups (1st episode

psychosis patients ; chronic schizophrenics & main control group) on both right & left sides. Each couple of these three groups were compared regarding right & left sides. Chronic schizophrenics had the most significant smallest mean hippocampal volumes (*2551.80 ± 492.18 mm³* on the Rt. side & 2518.84 ± *519.58 mm³* on the Lt. side) than 1st episode psychosis patients (*3308.80 ± 465.66 mm³* on the Rt. side & 3175.08 ± *697.27 mm³* on the Lt. side) whose right & left hippocampi were also significantly smaller than right & left hippocampi of the main control group (*3824.55 ± 187.00 mm³* on the Rt. side & 3833.60 ± *266.92 mm³* on the Lt. side) (**MRI images 1-3**). On both right & left sides, the differences were highly statistically significant (*p = **0.000***) Figure (**1**).

Hippocampal volumes in patients receiving either typical or atypical antipsychotic drugs are listed in table (**4**). Chronic schizophrenic patients on atypical antipsychotics had larger Rt. & Lt. mean hippocampal volumes than those on typical antipsychotic drugs. The difference was statistically significant (***p=0.011***) on the left, but, was **marginally** significant (***p=0.052***) on the right side.

Correlation between significant variables inside each of the patients' groups separately:

Table (**5**) demonstrates Spearman's rank correlation coefficient value for the relationship between some of the quantitative significant variables inside **1st episode psychosis patient group**. The results were as follows:-

- The table shows a negative significant correlation between age & score of general psychopathology (of PANSS), and between age and Rt. hippocampal volume.
- Duration of illness did not correlate with either severity of symptoms or the hippocampal volume.
- Total PANSS score was directly correlated to both sub-scores of PANSS and CGI scores. A significant positive relation was found between both the **total** PANSS score as well as score of **negative symptoms** and the Rt. hippocampal volume (p=0.032; p=0.002), respectively, whereas the correlation was significantly negative with the Lt. hippocampal volume (p=0.04; p= 0.03), in order.
- We also found, high significant correlation between scores of CGI & all scores (total & sub-scores) of PANSS in 1st episode psychosis patients (p< 0.01).
- There was no significant correlation between Rt. & Lt. hippocampal volumes in the acute group of patients, but they were directly related in the chronic group (i.e. reduction of the hippocampus in one side was significantly related to the reduction of the other side).

Table (**6**) shows the correlations between some of the quantitative significant variables in **chronic schizophrenic patient group**:-

- Age was directly related with the total severity of symptoms especially the positive symptoms. Age also is inversely related to hippocampal volumes (the more the age, the more reduction in hippocampal volumes in chronic schizophrenics); the correlation was significant on Lt. side but not on Rt. side.

- There were highly significant positive correlations between the total score of PANSS & the severity of the 3 subsets of the sc
- ale as well as CGI score ($p<0.01$).
- Lt. hippocampal volume had a direct correlation with total PANSS score & with the severity of positive symptoms.
- Rt. hippocampus volume was not correlated significantly to any of the parameters employed in chronic schizophrenic group.

Table (1): Socio-demographic data of the four studied groups:-

Variables	1st episode psychosis patients *(n=25)*	Control group of 1st episode patients *(n=20)*	Chronic schizophrenic patients *(n=25)*	Control group of chronic patients *(n=20)*	Values (t / χ^2 / LLR)	p value
Age (*Mean ± SD*)	*29.9 ± 9.1*	*28.3 ± 8.2*	*45.9 ± 8.0*	*44.5 ± 7.8*	t^1 0.64 t^2 0.56	P^1 0.53 P^2 0.58
Gender						
Male	12	10	16	12	1.71	0.64
Female	13	10	9	8		
Current level of education						
No formal education	0	0	4	0		
Primary school	2	2	5	5		
Preparatory school	5	4	3	3	16.93	0.15
Secondary school	15	12	9	8		
University	3	2	4	4		
Marital status						
Single	16	9	16	2		
Married	6	10	7	14		
Separated	3	0	0	2	31.16	0.002*
Widowed	0	0	0	1		
Divorced	0	1	2	1		
Family history of mental disorders						
Yes	9	-	15	1	2.89	0.09
No	16	-	10	-		

* Correlation is significant at the 0.05 level

P^1, t^1 = Independent sample t-test &correlation between 1st episode psychosis patients and their control.

P^2, t^2 = Independent sample t-test &correlation between chronic schizophrenic patients and their control.

χ^2 = Chi-square (Kruskal Wallis test).

LLR = Likelihood Ratio.

Table (2): Clinical data of patients with 1st episode psychosis, versus patients with chronic schizophrenia:-

Scales		1st episode psychosis patients *(Mean ± S.D.)*	Chronic schizophrenic patients *(Mean ± S.D.)*	t	p value
PANSS Scores	Total	*92.7 ± 22.5*	*88.1 ± 20.1*	0.76	0.45
	Positive	*20.3 ± 7.2*	*23.9 ± 10.0*	1.44	0.16
	Negative	*27.8 ± 8.2*	*25.4 ± 7.3*	1.13	0.27

	General psychopathology	*44.6 ± 11.5*	*38.9 ± 10.7*	1.81	0.08
Clinical Global Impression Scale severity		*5.7 ± 1.3*	*5.1 ± 1.0*	2.13	0.06

PANSS= Positive & Negative Symptoms Scale

t = t-value (Independent sample t-test)

*** Correlation is significant at the 0.05 level (p value)**

Table (3): Hippocampal volumes (mm^3) in patients with 1st episode psychosis, chronic schizophrenics, & their control groups:-

Group	Rt. Hippocampal Volume			Lt. Hippocampal Volume		
	Mean ± S.D. *(mm^3)*	*t*	*p* value	*Mean ± S.D.* *(mm^3)*	*t*	*p* value
1st episode psychosis patients *(n=25)*	*3308.80 ± 465.66*	4.97	0.000**	*3175.08 ± 697.27*	4.46	0.000**
Control group of 1st episode psychosis patients *(n=20)*	*3826.85 ± 209.02*			*3879.55 ± 332.34*		
Chronic schizophrenic patients *(n=25)*	*2551.80 ± 492.18*	12.06	0.000**	*2518.84 ± 519.58*	11.41	0.000**
Control group of chronic patients *(n=20)*	*3822.25 ± 167.55*			*3787.65 ± 177.07*		

*** * Correlation is significant at the 0.01 level (p value)**
t = t-value (Independent sample t-test)

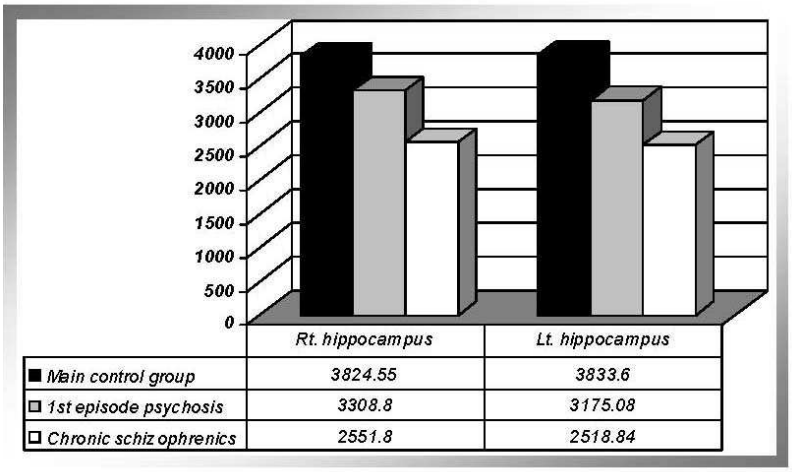
Table (4): Effects of antipsychotics (typical / atypical) on Rt. & Lt. hippocampal volumes, in chronic schizophrenic patients:-

Antipsychotics	Rt. Hippocampal Volume			Lt. Hippocampal Volume		
	Mean ± S.D. *(mm^3)*	*t*	*p* value	*Mean ± S.D.* *(mm^3)*	*t*	*p* value
Typical *(n=9)*	*2357.33 ± 66.66*	2.03	0.052	*2180.78 ± 424.64*	2.75	0.011*
Atypical *(n=16)*	*2661.19 ± 591.41*			*2709.00 ± 478.15*		

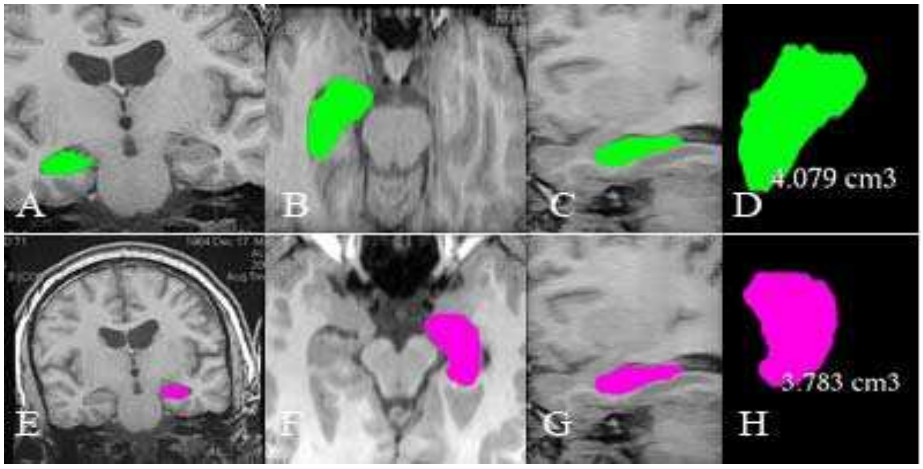
*** Correlation is significant at the 0.05 level (p value)**

t = t-value (Independent sample t-test)

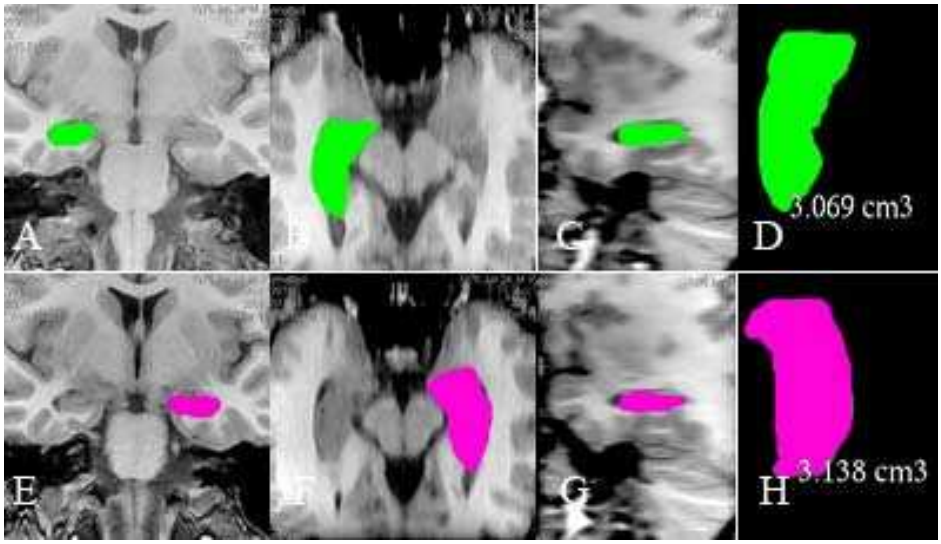
Figure (1): Comparison between Rt. & Lt. hippocampal volumes (mm^3) in main control group (*n=40*); 1st episode psychosis patients (*n=25*), & chronic schizophrenics (*n=25*).



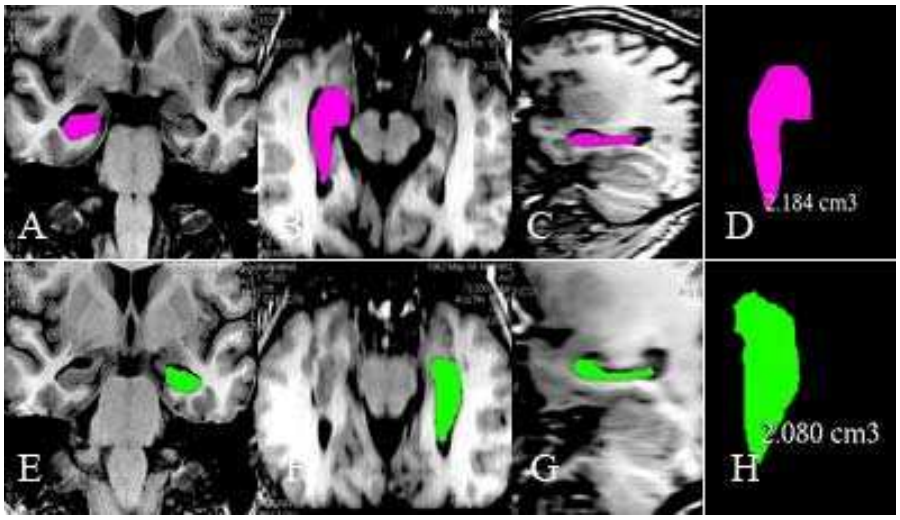
	Rt. hippocampus	Lt. hippocampus
Main control group	3824.55	3833.6
1st episode psychosis	3308.8	3175.08
Chronic schizophrenics	2551.8	2518.84



MRI images (1): <u>Hippocampal volume in a healthy subject</u>. A, B, C & E, F, G are coronal, axial, & sagittal reformatted images from the 3D T1 SPGR. Images of the right side (above) shaded with green & left side (below) shaded with pink. The hippocampus shaded with green & pink, D, & H shows the calculated volume of the hippocampus.



MRI images (2): Hippocampal volume in a 1st episode psychosis patient. A, B, C & E, F, G are coronal, axial, & sagittal reformatted images from the 3D T1 SPGR. Images of the right side (above) shaded with green & left side (below) shaded with pink. The hippocampus shaded with green & pink, D, & H shows the calculated volume of the hippocampus.



MRI images (3): Hippocampal volume in a chronic schizophrenic patient. A, B, C & E, F, G are coronal, axial, & sagittal reformatted images from the 3D T1 SPGR. Images of the right side (above) & left side (below) the hippocampus shaded with green & pink, D, & H shows the calculated volume of the hippocampus.

Table (5): Spearman's rank correlation coefficient value for the relationship between some of the quantitative significant variables inside **1st episode psychosis patient group**:-

Variables	*r–value & p value*	Age	Duration of illness in Days	Total score of PANSS	Score of positive symptoms	Score of negative symptoms	Score of general psycho-pathology	CGI severity	Rt. Hippocampal Volume
Age (years)	*r* *p*								
Duration of illness in Days	*r* *p*	.031 .88							
Total score of PANSS	*r* *p*	.15 .48	-.19 .42						
Score of positive symptoms	*r* *p*	.02 .94	-.08 .70	.84 .000**					
Score of negative symptoms	*r* *p*	.27 .19	-.23 .26	.91 .000**	.81 .000**				
Score of general psychopathology	*r* *p*	-.42 .04*	-.16 .46	.69 .000**	.46 .02*	.51 .01*			
CGI severity	*r* *p*	.06 .77	-.39 .05	.88 .000**	.83 .000**	.75 .000**	.53 .006**		
Rt. Hippocampal Volume	*r* *p*	-.58 .002**	-.05 .83	.43 .03*	.34 .10	.58 .002**	.12 .58	.33 .11	
Lt. Hippocampal Volume	*r* *p*	-.10 .63	-.13 .55	-.49 .04*	-.14 .50	-.43 .03*	-.16 .43	-.09 .67	.24 .24

PANSS = Positive & Negative Symptoms scale CGI = Clinical Global Impression Scale
r = r - value (Spearman's rho test).
*** Correlation is significant at the 0.05 level (p value)**
**** Correlation is highly significant at the 0.01 level**
(-) = negative correlation.

Table (6): Spearman's rank correlation coefficient value for the relationship between some of the quantitative significant variables inside **chronic schizophrenics group**:

Variables	*r–value & p value*	Age	Duration of illness in Years	Total score of PANSS	Score of positive symptoms	Score of negative symptoms	Score of general psycho-pathology	CGI severity	Rt. Hippocampal Volume
Age (years)	*r* *p*								
Duration of illness in Years	*r* *p*	.17 .41							
Total score of PANSS	*r* *p*	.47 .02*	.12 .55						
Score of positive symptoms	*r* *p*	.44 .03*	.48 .01*	.58 .002**					
Score of negative symptoms	*r* *p*	.16 .46	.25 .23	.52 .008**	.34 .10				
Score of general psychopathology	*r* *p*	.35 .09	.31 .12	.87 .000**	.31 .14	.70 .000**			
CGI severity	*r* *p*	.29 .16	.08 .69	.90 .000**	.27 .20	.73 .000**	.83 .000**		
Rt. Hippocampal Volume	*r* *p*	-.35 .08	-.05 .81	.30 .14	.31 .13	-.06 .76	.29 .17	.28 .17	
Lt. Hippocampal Volume	*r* *p*	-.52 .007*	-.24 .25	.39 .04*	.58 .003**	-.26 .21	.04 .85	.23 .27	.68 .000**

PANSS = Positive & Negative Symptoms scale
CGI = Clinical Global Impression Scale
r = r - value (Spearman's rho test).
*** Correlation is significant at the 0.05 level (p value)**
**** Correlation is highly significant at the 0.01 level**
(-) = negative correlation.

Discussion:

Reviews of MRI studies in schizophrenia consistently find reduction in hippocampal volume in patients compared with controls ***(Szeszko et al 2003; Wright et al., 2000; Whitworth et al 1998).*** This is true regarding the current study, where bilateral volume reduction of hippocampi was greater in both the acute and chronic patient groups than in control groups, with more reduction in chronic schizophrenic patients relative to drug- naïve patients in their acute stage.

While the above conclusion is supported by many studies such as ***Chakos et al.; 2005; Velakoulis et al 1999***, others didn't support such findings. ***Delisi et al. 1991*** found no difference in brain volume at illness onset; his findings were parallel to the conclusion of ***Gur et al 1998*** - in his longitudinal prospective study - who didn't find differences in volume reduction between first episode patients and chronic schizophrenics as compared to controls. The differences in findings between studies

were mainly explained by methodological difficulties with thick MRI slices.

The previous results raise a question, if structural hippocampal changes are neuro-developmental or neurotoxic in nature?

In the current study, the presence of bilateral hippocampal volume reduction and more severe illness in first episode psychosis group of patients could suggest a genetic risk (neuro-developmental), while more reduction in chronic group may support illness neurotoxic effect. The hippocampal volume reduction was not related to duration of illness in both patient groups. Our conclusion coincides with that of ***Chakos et al 2005; John et al. 2002***; & ***Nelson et al 1998***. Many other studies support the hypothesis of genetic vulnerability e.g. ***Csernansky et al 2002***, who concluded that abnormalities in shape and asymmetry were present at onset but was not correlated with either severity or duration of illness, findings suggestive of genetic risk. Also, ***Beng Choon Ho et al 2005*** reported that hippocampal morphology and volume were not associated with duration of untreated initial psychosis, supporting the neuro-developmental hypothesis. ***Velakouilis et al 1999*** reported that left sided volume reduction was present in both groups (acute and chronic), while right side volume reduction increased with chronicity which raised two possibilities either right sided specificity for chronicity or volume reduction is more likely to have chronic course.

The current results may also support the neurotoxic hypothesis, where patients with chronic schizophrenia- in spite of being treated and have less severe psychosis - had smaller hippocampal volumes than patients in their first episode psychosis. The neurotoxic hypothesis was supported by some studies (Leiberman 1999; Delisi 1997; Miller 1989) denoting the illness effect with time.

The neurotoxic hypothesis may be true if the degree of volume reduction was correlated with variables such as chronicity, treatment variable, psychopathological severity and socio-demographic data as well as clinical variables.

Regarding age effect: In the present study, age was negatively related to the hippocampal volume in the left but not the right hippocampus. The same was reported by ***Velakoulis et al 1999***. In our findings, the age has only a differential effect being directly related to the reduction in the volume of the right hippocampus in the acute group, and to the left hippocampal volume reduction in the chronic group. This differential effect was supported by the findings of ***Chakos et al. 2005; & Seidman et al 2002.***

Gender also had a differential effect on chronic schizophrenic patients but not on acute group, were female patients were significantly associated with more left hippocampal volume reduction. This may suggest high vulnerability of female patients to structural brain changes with chronicity. The differential effect of gender was also reported by ***Szeszko et al 2003 & Szeszko et al 2002*** while no gender effect was reported by ***Velakoulis et al 1999***.

An interesting finding in the current study was that chronic schizophrenic patients on atypical antipsychotics had larger Rt. & Lt. mean hippocampal volumes than those on typical antipsychotic drugs. A finding which may suggest that patients treated with atypical antipsychotics may lose less hippocampal tissue if given such treatment

early after illness onset. Similar findings were reported by ***Chakos et al. 2005; & Lieberman et al 2005*** who assessed brain volume changes in first episode psychosis, haloperidol treated patients had significant reductions in gray matter volume, whereas Olanzapine group had not. There was no correlation between dose and brain volume changes. Preclinical studies have suggested that atypical antipsychotics could have a neurotrophic or a neuroprotective effects ***(Halim et al 2004; Bai et al 2003).***

What is unique in our result is the differential effect for the PANSS subscales. First episode patients with more severe negative symptoms had smaller left but not right hippocampi. Similar result was reported by ***Sigmundsson et al 2001***.Moreover; patients with high positive symptoms score had smaller left hippocampi volume in chronic patients. The above two findings may indicate specificity of left sided hippocampus for differential illness severity effect.

From above we can conclude that illness severity may have differential effect on hippocampal volume rather than illness duration. In contrast to ***Hohn et al. 2002*** who did not find a significant relation between illness severity and hippocampal shape and asymmetry.

Lack of effect of illness duration on hippocampal volume with differential effect of age, gender and severity may suggest neuro-developmental hypothesis, while volume reduction in chronic group indicate that neurotoxic effect hypothesis is there to some extent. But still we can not conclude that these volumetric changes are specific to schizophrenia. The same suggestion was mentioned by ***Colter and Parianto 2002*** that brain changes found at onset or possibly after are not purely developmental and not specific for schizophrenia.

Conclusion & Recommendations:

- Bilateral hippocampal volume reduction was present in chronic more than acute patients and in both groups of patients than in control groups.
- Both neuro-developmental and neurotoxic hypothesis could be suggested. More longitudinal prospective studies are needed.
- Hippocampal reduction was not related to duration of illness.
- Age, gender and illness severity have differential effect on the volume of the right and left hippocampai.
- Atypical antipsychotic may have positive effect on hippocampal volume suggesting a neuroprotective effect and favoring early treatment. This conclusion can not be generalized, because of the small sample size &/or the hippocampal volume could be affected by other combinations of different psychotropic drugs used by chronic patients during their past years of illness.

This speculation needs prospective longitudinal study and more sophisticated techniques as well as big size sample of patients, and normal healthy control.

Limitations:

1. The current study lack a sample size sufficient to test genetic &/or neurotoxic hypotheses.
2. In spite of being a cross-sectional study, as we did not follow–up the acute patient group to know their final diagnosis, yet, a significant bilateral

reduction of the hippocampi was detected during this early stage of illness. This may suggest a relation between hippocampal reduction and the development of psychosis in general, but not specifically for schizophrenia.

3. We couldn't adjust the hippocampal volume with the whole brain volume because of technical difficulties.

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Authors:

El Tayebani M.
Lecturer of Psychiatry
Faculty of Medicine
Alexandria University

Abdel-Azim Kh.
Lecturer of Psychiatry
Faculty of Medicine
Ain Shams University

El Gamal M.
Lecturer of Psychiatry
Faculty of Medicine
Cairo University.

Ahmad:Kh
Lecturer of Radiology
Faculty of Medicine
Ain Shams University, Cairo.
e-mail: dr_khaled68@hotmail.com

Address of Correspondence:

Abdel-Azim: Kh
Lecturer of Psychiatry,
Faculty of Medicine
Ain Shams University

e-mail: khaledazima@msn.com

Difference in Obtaining Sexual History among Residents of Ain Shams University Hospitals

Reda M. and Hussein H.

Abstract

Sexuality is a complex process; it incorporates family, social and religious beliefs, its expression intimacy remains important throughout life span. Many patients have questions and concerns about their sexuality. Medical illnesses and medications may alter the sexual ability which requires physicians to inquire about any sexual dysfunction in their patients. Attitude of doctors vary regarding obtaining sexual history and determining any dysfunction. For it requires certain training and skills. Determine Ain Shams residents' attitude regarding obtaining sexual history from their patients. A special questionnaire was designed in 3 parts, part I: covering sexual dysfunction history obtaining in general and in detail, part II: reasons for not obtaining sexual history, part III: determine knowledge about effect of illness and medication on sexual function. 100 questionnaire sheets were randomly distributed among residents of Ain Shams University in different departments. Response rate 49%, Within the medicine group 24.5% were in the dermatology department, 16.3% in the general medicine department, 4.1% in cardiology, 8.1 % in neuropsychiatry; whereas within the surgery group 22.4% were in gynecology, 16.3% in general surgery, plastic, vascular and orthopedic surgery and 6.1% in urosurgery department. 51% obtained detailed sexual history being highest in dermatology & endocrinology 100%, followed by urology & urosurgery 100% then gynecology & obstetrics 54.5%. Asking about use of sexually enhancing drugs in urology & urosurgery 100% dermatology & endocrinology92.3% followed by gynecology & obstetrics 36.4%. Female sexual history (pubertal and contraceptive), showed highest level of acceptance by residents, gynecology & obstetrics, followed by neuropychiatrists. Reasons for not obtaining sexual dysfunction history not included patient data sheet, finding this topic unimportant. Discrepancy in the attitude of Ain-Shams University hospital residence towards obtaining sexual dysfunction history reflects the need for a curriculum change to high light the importance of sexual history from patients and care should be paid toward managing reasons for not engaging in providing the patient with needed data concerning their sexual life

Introduction

Sexuality is a complex process, coordinated by the neurologic, vascular and endocrine systems. Individually, sexuality incorporates family, societal and religious beliefs, and is altered with aging, health status and personal experience. In addition, sexual activity incorporates interpersonal relationships, each partner bringing unique attitudes, needs and responses into the coupling. A breakdown in any of these areas may lead to sexual dysfunction **(Phillips 2000).**

Sexuality and its manifestations constitute some of the most complex of human behavior. The expression of sexuality and intimacy remains important throughout life span **(Roodsari et al, 2005).**

Many patients have questions or concerns about sex, but few talk directly about the subject with their physician. Including a

sexual history during the physician-patient encounter is one way to indicate to the patient that discussing sexual concerns is appropriate **(Driscoll.et al, 1986).**

Sexual dysfunction is common at any age. The most common problems are loss of sexual drive, anorgasmia, vaginismus in women, and erectile failure and premature ejaculation in men. Up to 38% of women report anxiety and inhibition during sexual activity, 16% complain of lack of pleasure, and 15% have difficulties reaching orgasm. Up to 40% of middle aged men report some kind of sexual dysfunction. The dysfunction may be purely psychological or physical but is usually a mixture of the two **(Lewin & King 1997)**

Sexual dysfunction is a particular problem for physically ill or handicapped people. Half of middle aged men with insulin dependent diabetes report erectile dysfunction. Between 50% and 90% of patients with multiple sclerosis will develop sexual difficulties. Dyspareunia is twice as prevalent in women with inflammatory bowel disease as in healthy matched controls **(Lewin & King 1997).**

Attitudes to sexuality in society are becoming more relaxed, and people expect their doctor to be able to ask them about sexual problems. Many doctors, however, find it difficult to discuss the sexual details of their patients' lives **(Lewin & King 1997).**

Many people believe that their doctor is a suitable professional in whom to confide their sexual difficulties, but few doctors are taught how to manage them **(Ross & Channon-Little, 1991)**

The lack of undergraduate and postgraduate training in managing sexual problems is one reason for the under-recording in general practice notes of consultations about sexual problems. The medical model of history, examination, diagnosis, and treatment is a poor tool when faced with "dysfunction" of what is fundamentally a psychosomatic event—sexual activity and orgasm **(Whitmore, 2003).**

Primary care physicians, skilled in the treatment of medical and psychologic disorders, often feel unqualified to treat patients with sexual dysfunction. However, with an understanding of sexual functioning and application of general medical and gynecologic treatments to sexual issues, sexual dysfunction may be effectively approached with the same skills. The latter includes obtaining a complete patient history, conducting a physical examination, application of basic treatment strategies, providing patient education and reassurance, and recommending appropriate referral when indicated **(Phillips 2000).**

Healthcare practitioners should be able to deliver sex information ranging from advising on sexually transmitted infections or sexual dysfunctions to helping people for whom sexual contact is difficult or who may have missed out on sex education. This does not mean that they have to book their patients a prostitute or conduct a sex education class, but they should know where to refer them **(Boynton 2004).**

We aimed to find out the attitude of residents of Ain Shams University towards obtaining a full and comprehensive sexual history as reflected upon the frequency of asking their patients.

Subjects and Methods:

After reviewing available literatures to cover possible questions needed to be asked **(Schmidt 1987, Naus 1989, Morris 1995, Fisher 1998)**, a self administered

questionnaire, in order to avoid forced best answer bias, was designed to be filled by residents of different specialties of Ain Shams University Hospitals. It was composed of three parts addressing the following:

1. If residents positively obtain general and/or detailed sexual history (14 questions).
2. The possible reasons for not obtaining sexual history, those possibilities were designed based on available literatures (7 reasons).
3. Physician awareness of effect of medical illness and medications on sexual performance (2 items).

A total of 100 sheets were randomly distributed on residents of different specialties from Ain Shams University hospitals.

Results:

Forty nine residents, nearly half of those who entered the study, responded by completing a self administered questionnaire about sexual history taking (see appendix)

Descriptive data are summarized in the following table:

Table 1: descriptive data of the sample:

		n (%)
Marital status	single	36 (73.5%)
	married	13 (26.5%)
Department	surgery	21 (42.9%)
	medicine	28 (57.1%)
		mean (±std.)
Duration of residency in months		18.57 (±10.0)

Within the medicine group 24.5% (n = 13) were in the dermatology department, 16.3% (n = 8) in the general medicine department, 4.1% (n = 2) in cardiology, 8.1 % (n = 4) in neuropsychiatry; whereas within the surgery group 22.4% (n = 11) were in gynecology, 16.3% (n = 8) in general surgery, plastic, vascular and orthopedic surgery and 6.1% (n = 3) in urosurgery department.

Of the residents who handed their questionnaires, only one (2%) resident in general surgery department failed to ask about any of the questions of sexual history obtaining whether sexual cycle or female sexual history. On the other hand, only 2 (4.1%) of the residents, one in gynecology & obstetrics and the other in endocrinology ask about all the questions of sexual cycle and female sexual history.

67.4% (n = 33) ask at least 3out of 5 questions about female sexual history. On the other hand, 36.8% (n = 18) ask at least 5 out of 9 questions about sexual cycle and satisfaction. 63.5 (n=31) ask less than 7 out of 14 questions.

Residents were compared regarding their attitude to sexual history obtaining using chi square test and results were as follows.

Table 2: Number and percentage within department of residents who responded "yes" for Sexual cycle questions:

	dysfunction	desire	excitement	orgasm	resolution	PCP
Endocrine & dermatology.	13 (100%)	11 (84.6%)	12 (92.3%)	11 (84.6%)	5 (38.5%)	8 (61.5%)
Urology & urosurg.	3 (100%)	2 (66.7%)	1 (33.3%)	1 (33.3%)	0	1 (33.3%)
Neuropsychiatry	0	0	0	0	0	0
cardiology	0	0	0	0	0	0
General medicine	1 (12.5%)	0	0	0	0	0
General surgery	2 (25%)	1 (12.5%)	0	0	0	0
Gynecology & obstetrics.	6 (54.5%)	5 (45.5%)	1 (9.1%)	1 (9.1%)	1 (9.1%)	9 (81.8%)
Total yes	25 (51%)	19 (38.8%)	14 (28.6%)	13 (26.5%)	6 (12.2%)	18 (36.7%)
X2	28.58	23.89	36.75	32.23	11.90	25.85
P value	0.001	0.001	<0.001	<0.001	0.06	<0.001

PCP= post coital problems

In detailed sexual history obtaining, there has been a very highly significant association between the specialty of residency and obtaining sexual cycle history except for resolution phase where association was not statistically significant. It was obvious that residents of dermatology & endocrinology followed by urology & urosurgery then gynecology & obstetrics were the most frequently group obtaining detailed sexual history. Neuropsychiatry and cardiology residents do not ask a detailed sexual history (table 2).

Detailed sexual cycle history obtaining results showed that asking about sexual dysfunction was the main concern for residents (n=25, 51%) while the least to be questioned is the resolution phase (n=6, 12.2%).

Asking about frequency and satisfaction of partners and the use of sexually enhancing drugs in history obtaining the results were as follows:

Table 3: Number and percentage within department of residents who responded "yes" for Frequency and satisfaction:

	Frequency	satisfaction	SED
Endocrine & dermatology.	13 (100%)	11 (84.6%)	12 (92.3%)
Urology & urosurg.	1 (33.3%)	1 (33.3%)	3 (100%)

Table (2): continue:

	Frequency	satisfaction	SED
Neuropsychiatry	0	0	0
cardiology	0	0	0
General medicine	0	0	2 (25%)
General surgery	0	0	0
Gynecology & obstetrics.	9 (81.8%)	4 (36.4%)	4 (36.4%)
Total yes	23 (46.9%)	16 (32.7%)	21 (42.9%)
X2	39.75	26.69	14.89
P value	<0.001	<0.001	0.02

SED= sexually enhancing drugs

Regarding questioning frequency and satisfaction of sexual behavior of the patient, there has been a very highly significant association between the specialty of residency and questioning except for use of sexually enhancing drugs where association was statistically significant (P=0.02). It was again obvious that residents of dermatology & endocrinology followed by urology & urosurgery then gynecology & obstetrics were the most frequently group tackling these issues. Neuropsychiatry, cardiology and general surgery residents do not pose those questions (table 3).

As shown in the table, while gynecologists and obstetricians are more interested in the frequency of sexual intercourse (n=9, 81.8%), urologists, urosurgeons (n=3, 100%), endocrinologists and dermatologists (n=12, 92.3%) are more concerned with the use of sexually enhancing drugs.

Table 4: Number and percentage within department of residents who responded "yes" for female sexual history:

	menarche	Duration of menses	contraception	Involve of partner in choice	Satisfaction in Presence contraception
Endocrine & dermatology.	7 (53%)	9 (69.2%)	12 (92.3%)	4 (30%)	4 (30.8%)
Urology & urosurg.	2 (66.7%)	2 (66.7%)	1 (33.3%)	0	1 (33.3%)
Neuropsychiatry	4 (100%)	3 (75%)	4 (100%)	1 (25%)	0
cardiology	0	1 (50%)	2 (100%)	1 (50%)	0
General medicine	7 (87.5%)	8 (100%)	8 (100%)	1 (12.5%)	0

Table (3) continue

General surgery	5 (62.5%)	4 (50%)	2 (25%)	0	0
Gynecology & obstetrics.	11 (100%)	11 (100%)	11 (100%)	6 (54.5%)	1 (9.1%)
Total yes	36 (73.4%)	38 (77.5%)	40 (81.6%)	13 (26.5%)	7(14.3%)
X2	14.89	10.59	28.39	9.89	8.56
P value	0.02	0.1	<0.001	0.12	0.2

Regarding questions specific for female menstrual cycle and contraception, there has been a very highly significant association between the specialty of residency and questioning the use of contraception where general surgery and urosurgery were the least to ask. A statistically significant association existed between questioning the time of menarche and residency where none of the residents of cardiology ask about it. On the other hand, there has been no statistically significant association between questioning involving partner in the choice of the contraceptive method or sexual satisfaction in the presence of contraception and site of residency. It is worth mentioning that those two issues are the least concerned by the residents altogether (table 4).

Part two of the questionnaire was addressing why residents don't take sexual history. Out of 7 reasons, 21 (42.9%) did not mention a reason. Cultural boundaries and embarrassment were not a cause for not asking by any of the residents. Other reasons that were mentioned by residents are included in (table 5).

Table 5: Number and percentage within department of residents who responded "yes" for Reason for not asking

	sheet	**Un-import.**	**Know.**	**wording**	**Oppo. sex**
Endocrine & dermatology	1 (7.7%)	0	0	1 (7.7%)	0
Urology & urosurg	2 (66.7%)	0	0	2 (66.7%)	0
Neuropsychiatry	2 (50%)	1 (25%)	1 (25%)	1 (25%)	0
cardiology	0	0	0	0	0
General medicine	5 (62.5%)	1 (12.5%)	1 (12.5%)	3	1 (12.5%)
General surgery	8 (100%)	1 (12.5%)	1 (12.5%)	1 (12.5%)	0
Gynecology & obstetrics.	3 (27.3%)	0	0	1 (9.1%)	0
Total yes	21 (42.8%)	3 (6.12%)	3 (6.12%)	9 (18.4%)	1(2%)
X2	21.86	21.05	5.50	8.99	5.23
P value	0.001*	0.002*	0.48	0.17	0.51

Un-import.: Un-important

Know. : Knowledge

Opps.sex: Opposite sex

Of all who do not ask most of the questions, 21(42.8%) residents, mostly in the general surgery urosurgery, general medicine and neuropsychiatry do not as it is not included in patient history sheet, and 3(6.12%) residents, mostly in neuropsychiatry, general medicine and general surgery due to thinking it is unimportant or irrelevant to the problem of the patient. Those two factors are highly significantly associated with department of residence.

In part three of questionnaire that determines residents' knowledge about impact of illness and medication prescribed on sexual life of patients, the results were as follow

Table 6: Number and percentage within department of residents who responded with "yes" for Knowledge about impact of:

Department	sexual dysfunction on patient condition	prescribed drug on sexual life
Endocrine & dermatology.	12 (92.3%)	12 (92.3%)
Urology & urosurg.	1 (33.3%)	1 (33.3%)
Neuropsychiatry	0	0
cardiology	0	0
General medicine	0	0
General surgery	0	0
Gynecology & obstetrics.	8 (72.7%)	8 (72.7%)
Total yes	21	21
X2	33.59	33.59
P value	<0.001	<0.001

Knowledge about the impact of sexual dysfunction on patient medical condition and the effect of prescribed medication on sexual life of the patient was highest in endocrinology and dermatology departments followed by gynecology & obstetrics residents, then urologist. Association between Knowledge and specialty of residency was of a very high statistical significance

Discussion

Sexual dysfunction is an important aspect of sexual health that is prevalent in the population but frequently goes undetected **(Humphery & Nazareth 2001).** Between 25 and 50 per cent of difficulties have an organic cause, the remainder are emotional or psychogenic in origin and most general practitioners will have to deal with these diagnostic challenges **(Richardson, 1989).**

Many patients have questions or concerns about sex, but few talk directly about the subject with their physician **(Driscoll et al, 1986).** In a recent global study of sexual attitudes and behaviors among people aged 40- 80 years, although almost half of all sexually active respondents had experienced at least one sexual problem, less than 19% of them (18.0% of men and 18.8% of women) had attempted to seek

medical help for their problem(s). Only 9% of men and women had been asked about their sexual health by a doctor in a routine visit during the preceding 3 years **(Moreira et al, 2005).**

Including a sexual history during the physician-patient encounter is one way to indicate to the patient that discussing sexual concerns is appropriate **(Driscoll et al 1986).** Yet, what is the attitude of residents to obtaining sexual history from patients? In an attempt to answer this question, hundred residents were asked to complete a self administered questionnaire on the issue (see appendix).

Response rate was 49% with only 49 residents were interested and handed back the questionnaire. Moreover, of those who responded a total of 31 residents (63.5%) ask less than half of the questions of sexual history. Our results indicate that residents in general have a disinterested attitude towards sexual history obtaining same as in a previous study by **(Humphery and Nazareth, 2001)** who studied general practioners (GPS) views on their management of sexual function. They found that out of 133 GPs who responded to the questionnaire, only 8 had special interest in sexual health. Most GPs (87) categorized sexual dysfunction as medium priority, 25 as high priority and 18 as low priority; three GPs did not respond to this query.

In our study, in general, asking about sexual problem showed marked discrepancy between residents of different departments. Sexual history is most frequently asked by residents of endocrinology, dermatology, urology and gynecology and obstetrics and least frequently asked by residents of cardiology, neuropsychiatry, general surgery and general medicine. This reflects that mainly it is not within the general system of data obtaining when dealing with patients, and that whether residents neglect or not obtaining the sexual history resulted from high awareness in certain departments and total lack of awareness in other departments.

When we asked further deep in sexual cycle, the results showed still that the main focus is on dysfunction and desire problems which is consistent with the most frequent sexual complaints, as **Nazareth et al, 2003** assessed prevalence of ICD-10 sexual disorders; the most common problems were erectile failure and lack or loss of sexual desire in men and lack or loss of sexual desire and failure of orgasmic response in women. It seems that physicians tend to ask and pay attention to problems which have a handy solution by which we mean sexually enhancing drugs. **Barrett, 2004** believes that staff in primary and secondary care, are not adequately trained in issues surrounding sexual intercourse, particularly interpersonal relationships, awareness, and respect of sexual difference. They also lack the confidence to communicate comfortably on sensitive topics. Unsurprisingly they either avoid discussion of the issue or do not handle it well.

Our suggestion is most likely based on the fact that asking about sexual practice frequency and satisfaction revealed that physicians give little interest to detect satisfaction, while the use of enhancing drugs was 100% in urology and urosurgeons, which may be explained by the pharmaceutical awareness programs. In recent years, the pharmaceutical industry has become very interested in sex as a focus for drug development and marketing. Many sexologists have embraced this new trend particularly because of greatly welcomed

research funding and increased professional opportunities (**Tiefer, 2000)**. That point's to the fact that pharmaceutical companies are playing major role in shifting physician's attitude towards asking questions to their patients. On the contrary, gynecologists and obstetricians are more interested in the frequency of sexual intercourse (n=9, 81.8%). This can be explained by their concern about inappropriate timing of intercourse and ovulation as a cause of infertility.

Again asking about involvement of partner in choice of method of contraception and sexual satisfaction in the presence of a specific contraceptive method was the most overlooked. The neglect of this most important humanistic issue may be the main cause of non compliance on contraception and of contraceptive failure in many circumstances.

Total of 31 residents (63.5%) of the sample ask less than half of the questions of sexual history, and they attributed it to not being included in the master history taking sheet, finding this topic un-important or irrelevant and lack of finding the proper wording to ask In Arabic which indicates a lack of sexual health training in our university same as in many other health service providers world wide. **Whitmore** 2003 stated that "The lack of undergraduate and postgraduate training in managing sexual problems is one reason for the under-recording in general practice notes of consultations about sexual problems."

When asked about knowledge of impact of illness on sexual life, Knowledge was highest in endocrinology and gynecology & obstetrics residents, followed by urologist. This reflects that although there is a high level of knowledge, still the level of involvement in obtaining sexual history of patient shows reluctance or neglect in some aspects of sexual life.

This survey has its limitation, small size of sample due to lack of cooperation of residents, that may reflect their viewing sexual life as of minor priority, and another limitation was failure to determine exact number of questionnaires distributed to each department, which was reflected in lacking the exact drop out rate of each department, still the results may be indicative of the need to integrate sexual health in post graduate training, and emphasize the need to either obtain history or referral to specialized service provider.

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Authors:

Reda M.
Lecturer of Psychiatry
Institute of Postgraduate Childhood studies
Ain Shams University

Hussein H.

Lecturer of Psychiatry
Institue of Psychiatry
Ain Shams University

Short and Long Echo ^{1}H Spectroscopy in an Egyptian Sample of Patients with Obsessive-Compulsive Disorder

Maher K., Ibrahim A., Hussein H., Skaker N., Nassib A., El Shafei A. and Sadek H.

Abstract:

Several lines of investigation into the cause(s) of OBSESSIVE-COMPULSIVE DISORDER (OCD) have suggested that it is characterized by dysfunction within a basal ganglia-thalamocortical neuronal circuit ***(Modell et al, 1989; Insel 1992)***. Neuroimaging studies have the potential to increase our understanding of the connection between observable symptoms and associated neurobiology, and perhaps lead to improvements in treatment and in matching treatment to patient needs ***(Rauch, 2000)***.We aim to study the concentrations of various metabolites in the caudate nucleus for a hypothesized difference between both patients and control groups and between both sides within the patient group and to identify a relevant biomarker that is sensitive and specific that could enhance our understanding of the pathophysiology of OCD. Ten OCD patients, who were medication free for at least 6 weeks, were recruited from among persons seeking treatment at the institute of Psychiatry, Ain Shams University, Cairo, Egypt. They were assessed using Y-BOCS and compared to 5 matched healthy controls regarding 'H-MRS Spectroscopy data. NAA/Cho mean was lower on the left corpus striatum than right in patient group and results are statistically significant (t= 2.54, P= 0.03). Also, there is a trend towards an increased level of choline bilaterally in the patient group compared to controls and a negative and statistically significant correlation existed between Cho+Cr and symptom severity (r = -0.63, P = 0.04). Although not statistically significant, level of NAA/Cr is higher on both sides in cases rather than controls. Within the patient group, NAA/Cr is higher on the right than the left but there was no statistically significant correlation with symptom severity. There has been a trend to increased NAA relative to creatine in the corpus striatum supporting the theory of defective neuronal pruning. Increased choline in corpus striatum suggests that choline concentrations can be a sensitive and specific biomarker for OCD.

Introduction:

Obsessive compulsive disorder (OCD) is a prevalent, serious neuropsychiatric disorder ***(Koran et al, 1996)*** of unknown etiology. Several lines of investigation into the cause(s) of OCD have suggested that it is characterized by dysfunction within a basal ganglia-thalamocortical neuronal circuit ***(Modell et al, 1989; Insel 1992)***. Neuroimaging studies have the potential to increase our understanding of the connection between observable symptoms and associated neurobiology, and perhaps lead to improvement in treatment and in matching treatment to patient needs ***(Rauch, 2000)***.

Several investigators have attempted to delineate a neuroanatomic abnormality in OCD by measuring the size or assessing the structural integrity of presumably critical CNS structures. In particular, the corpus striatum has been the focus of a series of computerized tomographic (CT) and, more recently, structural magnetic resonance imaging (MRI) studies ***(Kellner et al, 1991; Scarone et al, 1992; Robinson et al, 1995; Aylward et al, 1996; Jenike et al, 1996; Rosenberg et al, 1997).*** The corpus striatum

has shown abnormalities in patients with OCD compared with normal subjects in several imaging studies ***(Hoehn-Saric and Benkelfat, 1994; Baxter et al, 1992; Schwartz et al, 1996)***. Studies have been remarkably inconsistent, with some finding reduced caudate size ***(Robinson et al, 1995; Rosenberg et al, 1997)***, another finding increased caudate size ***(Scarone et al, 1992)***, and some finding no differences ***(Aylward et al, 1996; Jenike et al, 1996)***. Positron emission tomography (PET) and single photon emission computerd tomography (SPECT) studies were carried to compare patients with OCD with healthy volunteers. The most consistent differences have been in the orbital gyrus and the head of caudate ***(Saxena et al, 2001; Whiteside et al, 2004)***. Functional magnetic resonance imaging (FMRI) studies during symptom provocation have revealed activation within the corpus striatum (specifically in the caudate) along with other brain regions (medial orbitofrontal cortex, anterior cingulate, amygdala) ***(Rauch et al, 1994; Breiter et al, 1996)***. Numerous studies have implicated the thalamus. MRI studies have shown increased thalamic gray matter in medication free adult OCD patients compared to controls ***(Kim et al, 2001)***. Magnetic resonance spectroscopy (MRS) imaging studies have found localized functional neurochemical marker alterations in the left and right medial but not lateral thalamus ***(Fitzgerald et al, 2000; Rosenberg et al, 2001)***.

More recently, researchers have begun using MRS to evaluate potential differences in regional brain metabolites between patients and healthy controls. MRS has been used primarily to measure concentrations of metabolites in brain tissue such as N-acetyl-l-aspartate (NAA; a marker of neuronal viability), combined glutamate and glutamine (Glx; a marker for excitatory neurotransmitters), choline (Cho; a marker of cell membrane turnover), myo-inositol (mI; involved in phospholipidmetabolism), and creatine (Cr; a marker of cellular energetics, commonly used as a reference level). ***(Whiteside et al, 2006)***.

Although no studies have found identical results, two have identified unilaterally decreased NAA in the striatum of adults with OCD ***(Ebert et al, 1997; Bartha et al, 1998)***, and two have identified increased absolute concentrations of choline bilaterally in the medial thalami ***(Rosenberg et al, 2001; Smith et al, 2003)***. Recently, it was found that the mean concentration of Cho/Cr was significantly higher in the OCD patients than controls, but only in the parietal white matter and parietal Cho/Cr was positively correlated with the severity of OCD symptoms ***(Kitamura et al, 2006)***. In addition ***Rosenberg et al, (2000)*** found that elevated Glx concentrations relative to water in the left caudate decreased after successful pharmacotherapy. Finally, compared to healthy controls, absolute levels of NAA have been shown to be increased in the right, but not left, dorsolateral prefrontal cortex ***(Russell et al, 2003)***.

It is thus obvious that variability in MRS results in OCD patients occurs on different scopes: there is a variation in the metabolites tested; and a variation in areas in which those metabolites are tested; and in the clinical condition in which those metabolites are tested, let alone variation in ethnicity. In this study, we tried to identify a relevant biomarker that is sensitive and specific and that could enhance our understanding of the pathophysiology of the

disorder and could also help to better define the phenotype in order to reduce heterogeneity in genetic studies as well as facilitate early detection and therapeutic intervention. We thus chose to start at the beginning and to study metabolite levels and concentrations in the corpus striatum of OCD patients who are medication free in an urban Egyptian community.

Material & methods

Ten OCD patients were recruited from among persons seeking treatment at the institute of Psychiatry, Ain Shams University, Cairo, Egypt. They were compared to 5 matched healthy controls with minimal demographic differences regarding age, gender, education and handedness.

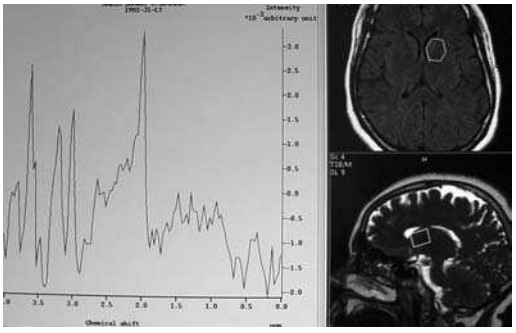
Subjects with OCD were diagnosed according to DSM-VI criteria by an experienced consultant using a semistructured interview [Structured Clinical Interview for DSM-IV-TR Axis I Disorders Clinical Version (SCID-CV)] ***(First et al, 1997)***. Comorbidity, family history, and other illness parameters (e.g. age at onset, duration of illness) were assessed at this time as part of the clinical interview, as was the patient's medical and prior treatment history. The subjects with OCD were required to have been medication free for a minimum of 6 weeks before the day of scanning, to be otherwise in good physical health, and to have no history of significant head injury or seizures. The same experienced interviewer determined the severity of OCD symptoms using Yale-Brown Obsessive-compulsive Scale (Y-BOCS) ***(Goodman et al, 1989)***. All OCD subjects were outpatients, and had no other current comorbid psychiatric disorder including tics. The healthy controls also underwent the SCID-CV clinical interview to ensure that they did not meet the criteria for any Axis I DSM-IV disorder.

The entire brain of each subject was imaged on the same magnetic resonance scanner and on the same day that the 'H-MRS data were acquired to primarily exclude presence of any organic lesion. 'H-MRS Spectroscopy data were acquired on a high-performance superconducting magnet 1.5 Tesla system (Philips Intera, ACS-NT system, Netherlands) MRI machine in a private center in east of Cairo, Egypt.

We used T2-weighted (5100/16, 96/2 [TR/effective TE/NEX]) obtained with a section thickness of 5 mm, gap of 1 mm, turbofactor 5, field of view (FOV) of 230 mm, and in-plane image matrix of 512x 196 imaging to locate the voxels for the ^{1}H-MRS studies. The selection of voxel position in the caudate nucleus was determined visually by examining the MR images in three orthogonal planes (sagittal, coronal, and axial) by the radiologists to ensure proper site of voxel placement. Spectra were then acquired from a 20 x 20 x 20-mm^3 volume of interest on both caudate nucleus. Water unsuppressed spectra were acquired with the use of a stimulated echo acquisition mode sequence (spectral bandwidth 1000 with TE=32 and 144 were acquired respectively).

All spectra were reviewed for quality, and spectra of insufficient quality were not included in the final analyses. Spectra of poor quality were identified by an increased line width of the water resonance (a measure of the field homogeneity in the region of interest). The metabolite concentrations were determined by using manufacturer supplied spectroscopy processing software, and manual determination of area under each of the metabolite peak in arbitrary units (integral

value) was performed focusing on N-acetylaspartate (NAA) and Choline (Cho) metabolites being the center of attention for a hypothesized difference, NAA/Cr, NAA/Cho ratios as well as Cho+Cr were also calculated.



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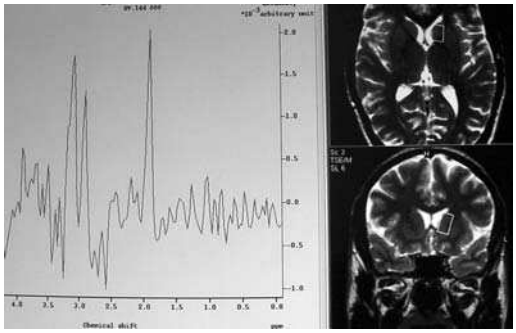

B

Fig. 1. (a) Short echo 'H-MRS Spectroscopy (TR=2000 msec, TE=32) acquired from a volume of interest (VOI) on head of left caudate nucleus. (b) long echo 'H-MRS Spectroscopy (TR=2000 msec, TE=144) with outlined white rectangle of VOI over left caudate nucleus.

Qualitative variables were described in number and percentages and mean ± standard deviation (SD) if quantitative. Student t and ANOVA tests were used when comparing quantitative data between 2 or more than 2 groups respectively. Pearson correlation coefficient was used as an indicator of correlation between 2 quantitative variables. P value was always set at 0.05. All data manipulation and statistical analyses were performed using SPSS (Statistical Package for Social Sciences) version 11.

Results:

Ten outpatients with OCD disorder (cases), who were medication free for at least 6 weeks; and 5 healthy controls who were matching regarding age, gender, social class and education were imaged using entire brain MRS spectroscopy after obtaining an informed consent.

OCD patients were psychologically assessed using Y-BOCS in order to determine symptom severity and phenomenology (mean score 28.2 ± 8.9). Among the patients group, 2 (13.3%) were mild; 2 (13.3%) were moderate; 6 (40%) were severe; 4 (26.7%) experienced only obsessions; 1 (6.7%) experienced only compulsions and 5 (33.3%) experienced mixed symptoms.

Testing if case and control groups were matching was done using chi square and independent sample t - test as appropriate. table (1).

Preliminary analysis of results showed that 50% (n=5) of patients had ratio of NAA/Cr to be *lower* on the left than on the right whereas in all subjects of the control group 100% (n=5) the ratio of NAA/Cr is *higher* on the left than on the right. Association between reversal and type of patient was not statistically significant as (X2=3.75, P=0.06). Similarly, within the patient

group, reversal was not associated with type of symptoms (X^2 = 2.2, P=0.3) or severity of the disorder (X^2=0, P=1).

Both cases and controls were compared, using independent sample *t*- test, regarding the NAA/Cr, NAA/Cho, Cho/Cr ratios, and Cr + Cho in the right and left corpus striatum and difference was not statistically significant. It is worth mentioning that NAA is increased relative to Cr used as a reference level in patients, compared to controls on both sides. Cho is also increased in patients, relative to Cr of contols on both sides as well.

In an attempt to detect any statistically significant difference in mean metabolite ratios between the right and left basal ganglia in patients, paired sample *t*- test was performed and results were not statistically significant for all ratios except for the the NAA/Cho, which was lower on the left side and the difference was of statistical significance. Table (3) shows the details.

We then attempted to detect any statistically significant correlation between various metabolite ratios on the left side and symptom severity and type using bivariate analysis and ANOVA where appropriate and found a negative and statistically significant correlation between the sum of creatine + choline, and symptom severity. Table (4) shows the details

Table (1): Both case and control groups are matching:

		Case N (%)	**Control N (%)**	**X^2**	**P**
GENDER	male	5 (50)	4 (80)	1.25	0.26
	female	5 (50)	1 (20)		
SOCIAL CLASS	middle	7 (70)	3 (60)	0.15	0.69
	low	3 (30)	2 (40)		
EDUCATION	Illiterate, primary	2 (20)	1 (20)	2.4	0.5
	preparatory	0 (0)	1 (20)		
	Secondary, technical	4 (40)	2 (40)		
	university	4 (40)	1 (20)		
HANDEDNESS	right	8 (80)	5 (100)	1.15	0.28
	left	2 (20)	0 (0)		
		Case Mean (±SD)	**Control Mean (±SD)**	***t***	**P**
AGE		33.5 (± 14.2)	32 (± 14.6)	0.19	0.8

Table (2) shows means and significance in details.

Table (2): Difference in mean metabolite levels in basal ganglia of both groups

	Case Mean (±SD)	Control Mean (±SD)	*t*	P
Rt. NAA	1.964 (± 2.356)	0.642 (± 0.393)	1.22	0.24
Lt. NAA	2.184 (± 2.934)	0.607 (± 0.430)	1.17	0.26
Rt. Choline	1.072 (± 1.251)	0.45 (± 0.252)	0.96	0.35
Lt. Choline	1.5232 (± 2.123)	0.485 (± 0.246)	0.95	0.36
Rt. NAA/Cr.	1.959 (± 0.895)	1.64 (± 0.192)	0.69	0.5
Lt. NAA/Cr	1.868 (± 0.778)	1.435 (± 0.12)	1.08	0.3
Rt. NAA/Cho	1.66 (± 0.3)	2.09 (±0.95)	-1.33	0.2
Lt. NAA/Cho	1.37 (± 0.25)	1.56 (± 0.16)	-1.38	0.2
Rt. Cho/Cr	1.17 (±0.43)	0.99 (±0.33)	1.13	0.3
Lt. Cho/Cr	1.42 (±0.93)	0.93 (±0.2)	1.44	0.2
Rt. Cr + Cho	2.07 (±2.669)	0.945 (± 0.372)	0.82	0.4
Lt. Cr + Cho	2.686 (± 3.814)	1.01 (± 0.454)	0.85	0.4

Table (3): difference between the right and left BG

		Right BG Mean (±SD)	Left BG Mean (±SD)	*t*	P
Cases	**NAA/Cr.**	1.959 (±0.895)	1.868 (± 0.778)	0.34	0.73
	NAA/Cho	1.66 (± 0.3)	1.37 (± 0.25)	2.54	0.03*
	Cho/Cr	1.17 (0.43)	1.37 (± 0.25)	1015	0.3
	Cr + Cho	2.07 (±2.669)	2.686 (± 3.814)	-1.59	0.14
Controls	**NAA/Cr.**	1.64 (± 0.192)	1.435 (± 0.12)	1.38	0.26
	NAA/Cho	2.09 (±0.95)	1.56 (± 0.16)	1.06	0.36
	Cho/Cr	0.99 (±0.33)	0.93 (±0.2)	0.15	0.9
	Cr + Cho	0.945 (±0.372)	1.01 (± 0.454)	-0.47	0.67

***indicates statistically significant result P≤0.05, P>0.05=non significant**

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Table (4): Correlation between symptom severity, phenomenology and Metabolite levels on the left BG of patient group.

Y-BOCS (Total)	NAA/Cr	NAA/Cho	Cr + Cho	Cho/Cr
r	0.34	-0.11	-0.63	0.368
P value	0.33	0.76	0.04*	0.3
Symptom severity	**Mean (±SD)**	**Mean (±SD)**	**Mean (±SD)**	**Mean (±SD)**
Mild	1.6 (±6.8)	1.5 (±0.15)	8.1 (±6.5)	1.11 (±0.2)
Moderate	1.6 (±2.7)	1.4 (±0.3)	1.5 (±2.1)	1.2 (±0.3)
Severe	2.0 9±1.0)	1.3 (±0.3)	1.3 (±1.5)	1.6 (±0.8)
f (P)	0.26 (0.77)	0.17 (0.84)	4.27 (0.06)	3.64 (0.08)
Phenomenology	**Mean (±SD)**	**Mean (±SD)**	**Mean (±SD)**	**Mean (±SD)**
Obsessions	1.5 (±0.2)	1.5 (±0.1)	4.8 (±5.5)	1.0 (±0.15)
Compulsions	1.2 (0)	1.5 (0)	0.9 (0)	0.8 (0)
Combined	2.3 (±0.96)	1.2 (±0.3)	1.5 (±1.5)	1.9 (±0.7)
f (P)	1.53 (0.28)	1.58 (0.27)	1.09 (0.38)	0.47 (0.64)

***indicates statistically significant result P≤0.05, P>0.05=non significant**

Discussion

Short echo proton magnetic resonance spectroscopy (1H-MRS) can be used to obtain information about several metabolites that are highly relevant to our understanding of the mechanisms of dysfunction within neuronal circuits in OCD and other neuropsychiatric disorders ***(Dager et al, 1992; Stanley et al, 1995)***.

Previous research has identified the corpus striatum as a potential area of the brain involved in OCD (***Schwartz et al, 1996; Bartha et al, 1998)***. More recently, researchers have begun using MRS to evaluate potential differences in regional brain metabolites between patients and healthy controls. MRS has been used primarily to measure concentrations of metabolites in brain tissue such as N-acetyl-l-aspartate, combined glutamate and glutamine, choline, myo-inositol, and creatine ***(Whiteside et al, 2006).***

It was found that N-Acetylaspartate levels from the left corpus striatum were significantly lower in the patients with OCD than in the comparison subjects (without differences in either left or right caudate volume between the two groups) which suggests reduced neuronal density in this region (***Bartha et al 1998)***. Also, two studies identified increased absolute concentrations of choline bilaterally in the medial thalami ***(Rosenberg et al, 2001; Smith et al, 2003).*** A third study found the

mean concentration of Cho/Cr was significantly higher in the OCD patients than controls, but only in the parietal white matter and parietal Cho/Cr was positively correlated with the severity of OCD symptoms ***(Kitamura et al, 2006)***.

The present study is the first study in Egypt to use MRS to image the corpus striatum in adults with OCD who are medication free for at least 6 weeks. We hypothesized that reduction of NAA concentrations within the corpus striatum as well as increased choline concentrations will be replicated.

NAA/Cr:

In our study, when we compared NAA/Cr ratios bilaterally in cases and controls, contrary to our hypothesis and to previously mentioned research in which NAA was reduced in corpus striatum (***Bartha et al 1998),*** or there has been no difference in left basal ganglia ***(Sumitani et al, 2007)*** or the lenticular nuclei ***(Ohara et al, 1999)***, there has been increased mean NAA/Cr ratio in patients. . However results were not statistically significant, probably due to small sample size. Our results were similar to a number of previous studies which found elevated NAA/Cr; in the right orbitofrontal white matter ***(Whiteside et al, 2006);*** right, but not left, dorsolateral prefrontal cortex ***(Russell et al, 2003).*** Increased relative levels of NAA found in the present study may be consistent with biologically based theories of OCD. Specifically, NAA is thought to be a marker of neuronal viability, and thus our finding may reflect an abundance of neurons. As such increased NAA/Cr in the corpus striatum could be consistent with neurobiological models of OCD postulating increased activity in the cortex ***(Saxena et al, 2001)*** and/or neurodevelopmental theories of OCD involving inefficient neuronal pruning ***(Rosenberg and Keshavan, 1998).*** Variability of results has been always the case in previous research which may be explained by the heterogenous etiologies of OCD.

Within the patient group, NAA/Cr levels were higher on the right similar to the previously mentioned studies ***(Whiteside et al, 2006; Russell et al, 2003).*** Again, results were not statistically significant.

In our study, there has been no statistically significant correlation between NAA/Cr and symptom severity or type, similar to previous research ***(Bartha et al, 1998)***. This was not the case in previous research where a significant negative correlation existed ***(Whiteside et al, 2006)***. Failure to detect significance in our research may be attributed to the small sample size.

Cho/ Cr & Cr+Cho:

Previous research found statistically significant increase of choline in left and right medial thalami ***(Fitzgerald et al, 2000; Rosenberg et al, 2001)***. Another study failed to detect any difference in Cho concentration in lenticular nuclei between 12 OCD patients and 12 healthy controls ***(Ohara et al, 1999).***

In our study, however, when we compared Cho/ Cr ratios, there has been a trend towards an increased level of choline bilaterally in patients compared to controls, a finding that is similar to most other research. Failure to detect statistical significance may be due to a small sample size.

The Cho spectra, as measured by proton magnetic resonance spectroscopy, primarily arise from glycerphosphocholine and phosphocholine metabolites of phosphocholine ***(Barker et al, 1994; Miller***

et al, 1996). Phosphotidyl choline is known to play a critical role in intracellular signal transduction ***(Ziesel, 1993)*** suggesting that altered Cho concentrations in patients with OCD may alter signal transduction and contribute to the pathogenesis of the disorder ***(Smith et al, 2003).***

When Cho concentrations were observed in OCD patients compared with both healthy control subjects and patients with major depression (MDD), significantly increased left and right medial thalamic Cho concentrations were observed in OCD patients compared with both healthy control subjects and patients with MDD whereas medial thalamic Cho concentrations did not differ significantly between patients with MDD and control subjects ***(Smith et al, 2003).*** This may represent a specific neurobiologic marker of OCD.

There is a negative and statistically significant correlation between the sum of creatine + choline, and symptom severity by YBOCS (r= -0.63, P=0.04). This finding is difficult to interpret and needs replication in further studies, especially in the presence of the positive non significant correlation between Cho/Cr ratio and symptom severity using the same scale (r=0.37, P=0.3).

NAA/ Cho:

Regarding NAA/ Cho which was not studied in previous research involving OCD and was a new variable to be tested, it was found that this ratio has been lower in patients compared to controls bilaterally. However, results were not statistically significant. Regarding laterality difference within the patient group, results were statistically significant (t=2.54, P= 0.03) with lower ratio in the left corpus striatum.

In a previous study, Single-voxel 1H MRS was performed in the left frontal lobe, the anterior cingulate gyrus and the left superior temporal lobe of non schizophrenic subjects at risk. Subjects were followed longitudinally to detect conversion to schizophrenia. A significant reduction of the metabolic ratios NAA/Cr and NAA/Cho in the left frontal lobe and of NAA/Cr in the anterior cingulate gyrus in both at-risk groups and in the schizophrenic patients compared with healthy controls was observed. Those at-risk subjects, who converted to schizophrenia within the observation period, had a higher Cho/Cr and a lower NAA/Cho ratio in the anterior cingulate gyrus compared with non-converters. NAA/Cr did not differ between converters and non-converters. Six at-risk subjects were taking antidepressants, two were taking antipsychotics. There was no difference in any metabolic ratio in any region between at-risk subjects with and without medication. It was concluded that the reduction of the neuronal marker NAA in the left prefrontal lobe and the anterior cingulate gyrus may represent a vulnerability indicator for schizophrenia in at-risk subjects, while elevated Cho in the anterior cingulate gyrus may be a predictor for conversion from the prodromal state to the full disease ***(Jessen et al, 2006).*** Patients with lower NAA/Cho ratio in this study may be a subgroup of OCD patients with poor insight (an item which was not analyzed) or who are a group susceptible to experience syndromal shift to schizophrenia if followed up.

Conclusion:

In this study, increased Cho in corpus striatum was found, replicating previous studies which suggests that Cho concentrations can be a sensitive and specific biomarker for OCD. Also, there has been a trend to increased NAA relative to

Cr in the corpus striatum, supporting the theory of defective neuronal pruning, a hypothesis that needs further study.

The small sample size, which is the main limitation of the study, may have restricted the power to detect differences. However, this is a common problem in the field of neuroimaging, given the expenses, equipment, and time required to complete studies, a potential solution is multi-site collaboration.

Recommendations:

More research in the field is mandatory with replication of the study using a larger sample size and testing the specificity and sensitivity of Choline as a marker of OCD by studying its changes in various psychiatric disorders.

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Authors:

Maher K.
Assistant Prof. of Radiodaignosis
Department of Radiodiagnosis
Ain Shams University

Ibrahim A.
Lecturer.of Radiodaignosis
Department of Radiodiagnosis
Ain Shams University

Hussein H.
Lecturer of Psychiatry
Instiute of Psychiatry
Ain Shams University

Skaker N.
Lecturer of Psychiatry
Institute of Psychiatry
Ain Shams University

Nassib A.
Lecturer of Psychiatry
Institute of Psychiatry
Ain Shams University

El Shafei A.
Lecturer of Psychiatry
Misr University of Science and Technology

Sadek H
Lecturer of Psychiatry
Institute of Psychiatry
Ain Shams University

Address of Correspondence:

Hussein H.
Lecturer of Psychiatry
Institute of Psychiatry
Ain Shams University

[illegible]

[illegible]

[illegible]

Role of Serotonin in Cue Exposure-Induced Craving in an Inpatient Sample of Egyptian Addicts

Haroun El Rasheed A., El Sayed N., Reda M, Hussein H.and Abou Ghalia A.

Abstract

Craving is one of the phenomena that attracted the attention of all researchers working in the field of substance use disorder due to its impact on abstinence and recovery. In this study we examined whether plasma level of (serotonin) 5-HT was altered during substance abuse and whether this measure would be related to craving. We also explored whether alterations in 5-HT activity differ between types of cue exposure (auditory and visual) in substance dependent patients during craving**.** Plasma measurements of 5-HT and assessments of craving were performed longitudinally in 10 Egyptian opium-dependent patients who were hospitalized for detoxification, at baseline, after answering craving questionnaire assessing the different craving inducing situations; and after exposing them to a video that is full of cues. These measures were compared with 5-HT levels obtained from equal number of matched controls. Baseline serotonin level for these patients had a mean of 39.31(± 49.23), which is highly significantly ($P<0.01$) lower than that for the healthy controls who had a mean of 194.1 (±10.65) with a significantly ($P<0.05$) sharp rise after completing the craving questionnaire to reach a mean of 113.85 (± 144.49). However, after watching a craving inducing film it reached a mean of 64.15 (± 80.15), yet this rise was not significantly different from baseline ($P>0.05$). Using student t-test for comparing those taking heroin intravenous to those using other modes of opium administration, it was found that there is a highly significant difference on comparing the serotonin levels after applying the questionnaire ($P=0.003$).It can be concluded that craving can be induced by auditory as well as visual cues; both are associated with changes in serotonin levels which is more evident with auditory cues. This proved that craving has biological basis: more studies are needed to clarify the picture as regards the different neurotransmitters involved and the role of pharmacotherapy in controlling these phenomena.

Introduction

Craving is a commonly used term to describe an intense desire for a substance or behaviour ***(Lingford-Hughes et al, 2006).*** It has been increasingly recognized to contribute to continued abuse and is believed to play an important role in relapse ***(Petrakis et al., 1999, Volkow et al, 2006)***, The main *Psychological* models of drug craving are classified broadly into three categories: (1) phenomenological models; based on clinical observation and description; these have been influential in classification systems of addictive disorders and in the development of pharmacological therapies; (2) conditioning models: based on conditioning theory; these have been influential in the development of cue exposure treatments; (3) cognitive theories; based on cognitive social learning theory: these have been influential in the development of cognitive therapies of addiction. It is concluded that no one specific theory provides a complete explanation of the phenomenon of craving ***(Drummond, 2001).*** However, its

underlying neurobiology is still not fully characterized.

Serotonin, the chemical 5-hydroxytryptamine (5-HT), is derived from the amino acid tryptophan and plays an important role in a wide range of physiological states, such as sexual behavior, intestinal functions, and affective states. As a chemical, serotonin has been launched to celebrity status in the past two decades because of its known involvement in depression, anxiety, and obsessive-compulsive disorders. Moreover, numerous data in both animals and humans have shown that the serotonergic system in the brain plays a key role in self-control behavior as a low serotonergic tone is well known to be frequently associated with impulsivity, auto-and hetero-aggressive behavior ***(Hamon, 2002).*** In substance abuse, acute administration of alcohol is known to stimulate 5-HT turnover, while chronic alcohol intake is reported to decrease 5-HT synthesis and release ***(Tollefson, 1989***). Reduced central 5-HT has been implicated in mediating alcohol preference in animals ***(LeMarquand et al., 1994).*** On the other hand, Cocaine use causes an initial increase in dopamine and serotonin neurotransmission that is largely responsible for the pleasurable and reinforcing effects of the drug. Dysregulation of these neurotransmitters during withdrawal plays an important role in craving. Recent research has focused on the use of dopamine and serotonin antagonists early in recovery to reduce cocaine craving ***(Smelson et al, 2004).***

Evidence supporting the effects of substance abuse on 5-HT function in humans is less consistent. Possible reasons may be the variation with dose, length of exposure or abstinence, heterogeneity of the clinical population, treatment with selective serotonin reuptake inhibitors and craving states ***(Naranjo and Knoke, 2001).***

A major methodological issue in studying peripheral levels of 5-HT and its relationship to central mechanisms, such as craving**,** is that it is unclear whether plasma 5-HT levels reflect corresponding changes in human brain. Certain metabolic differences are present between periphery and the brain in humans that may need to be considered during interpretation of data ***(Linnoila et al., 1986).*** Human studies have found similarities between the uptake, storage and release of 5-HT in neurons and blood platelets ***(Da Prada et al., 1988).***

In this study we tried to demonstrate the effect of cue exposure in different modalities in abstinent substance use disorder (dependence type) patients and if this can affect their serotonin blood levels. Since repeated central measurements of neurotransmitters in humans are expensive, invasive and technically difficult, we examined plasma 5-HT levels.

Methods:

Sampling:

The sample consisted of 10 opioid-dependent patients diagnosed according to DSM-IV criteria (American Psychiatric Association, 1994) who were hospitalized for detoxification; and an equal number of age and gender matched healthy volunteers, who served as the control population. The opioid-dependent subjects were recruited from a university affiliated inpatient addiction unit in Cairo, Egypt (ethically we can not expose patients to cues and let them go to see whether or not they are going to relapse, so we carried this research on

inpatients to avoid exposing them to relapse).

Procedure:

The study protocol was approved by the Staff committee of the hospital. All subjects gave written informed consent to proceed in the study. Opioid-dependent individuals who completed the study underwent a full psychiatric, medical interview and routine laboratory investigations for blood sugar, liver and kidney functions, in addition to screening for HIV as a part of the admission procedure of the addiction unit. Individuals with major depression, bipolar disorders or psychotic disorders, serious medical disorders and current illicit drug misuse, were excluded from the study.

Patients and controls then completed a craving questionnaire which represented the auditory cues. The questionnaire was prepared by using a multi-item scale in substance misusers. It included 8 variables, which were categorized as representing the high risk situations, moods or thoughts related to substance use that can induce craving if one imagines that he experiences. The questionnaire required 15 min to be complete. It was tested on 100 Egyptian patients and was found to have a Kappa coefficient of 0.92 which stands for excellent validity. Second, patients were exposed to a video that is full of cues related to substance abuse followed by measuring craving using visual analog scale. Serum serotonin level was obtained at baseline and after each step. However, on studying the effect of craving on baseline serotonin level, we decided to consider each patient's baseline as his own control.

Laboratory techniques

Thirty millilitres of venous blood were collected in glass tubes from subjects and controls. Blood samples were collected in the morning and transported to the laboratory on ice within 2 hours. For 5-HT assay, a good blood sampling technique, adequate platelet stabilization in the test tubes and rapid processing after collection reduced the possibility of platelet aggregation and activation that may stimulate 5-HT release and inflate the measured values (Beck *et al.*, 1993).

5-HTwas assayed using ELISA technique.

Statistical analysis

Data were analysed using SPSS for Windows. Release 11.0.1 (2001)

Data were summarized as frequencies and means. Comparing serotonin levels at different points of the study was done using Wilcoxon signed rank test since data proved to have a non-parametric distribution. To study the association between any of the craving high-risk situation and the changes in the serotonin level was done using ANOVA.

Results

We examined 10 opioid-dependent individuals (8males and 2 females). Their age ranged between 17-35 years with mean (25.6±6.13). They were more likely to be single 60%, 30% unemployed. No individuals proved positive for HIV. 90% had a history of opium as their main drug of dependence. Six of them were taking heroin i.v., while the remaining three were taking synthetic opiates. The duration of their drug dependence ranged from 3 up to 16 years (mean = 10.30 ± 4.83 years). The number of relapses experienced by these patients

ranged from one relapse till 8 relapses. They were all receiving treatment for the past one month in the form of carbamazepine (600 mg/day), chlorpromazine (300 mg/day), flouxetine (60 mg/day). Using Shapiro-Wilk test, sample proved to be non-normal in distribution.

The mean baseline 5HT level for the healthy control group was (m.194.1 ± 10.65 std.). Regarding that of patients, it was (m. 39.31 ± 49.23 std.). Using Mann- Whitney test, there has been a highly significant difference between baseline means being lower within the patient group ($P < 0.01$) despite receiving SSRI. Within the patient group, there has been a sharp rise after completing the craving questionnaire to reach a mean of 113.85 (± 144.49 std.). However, after watching a craving inducing film it dropped to reach a mean of 64.15 (± 80.15 std.). It is worth mentioning that all the patients reported very high craving on visual analog scale (8-10).

Comparing baseline serotonin levels with that after applying the craving questionnaire as well as to that following exposure to the craving-inducing film using Wilcoxon signed rank test, it was found that there is a significant difference on comparing the serotonin level after applying the questionnaire to the baseline serotonin level ($Z= -2.325$,$P= 0.02$) but not after watching the craving-inducing film to baseline 5 HT ($Z= -1.7$, $P=0.08$), however, there was a statistically significant difference between the serotonin levels after film and after craving questionnaire ($Z= -2.23$, $P=0.02$) as shown in table 1. There was no significant ($P>0.05$) on comparing males and females using Mann-Whitney test.

Using oneway ANOVA for comparing those taking heroin i.v. to those using other modes of administration (oral, sniffing), it was found that there is non significant difference on comparing the serotonin levels after applying the questionnaire as well as to that after watching the film ($P>0.05$).

There was a significant correlation ($P= 0.01$) between serotonin level after questionnaire and the number of relapses, while there was no such correlation between number of relapses and 5-HT level after the craving-inducing film. Regarding correlation between the duration of substance dependence and 5-HT level, there was a significant correlation ($P= 0.04$) with baseline serotonin level, while there was no such correlation with 5-HT level after the questionnaire or the film (table 2).

Regarding the confidence of the patients to control craving in the different situations tested by the craving questionnaire, results show that the situations that can be considered as high-risk situations were: physical discomfort (39.6±15.83), followed by pleasant times with others (41.6±22.33), and social pressure to use (42.6±20.46). Table (3)

Using ANOVA to study the possible role of each situation in relapse in our sample, it was found that physical discomfort, urges/temptations as well as testing personal control were highly significantly associated with relapse ($P=0.007$, $P=0.007$, and $P=0.009$ respectively). However, unpleasant emotions was only significantly associated with relapse ($P=0.013$). None was related to the duration of substance dependence.

Also when studying the association between any of the craving high-risk situation with the changes in the serotonin level after applying the questionnaire as well as that after exposure to the craving-inducing film,

it was found that having a high confidence to control physical discomfort was highly significantly associated with higher levels of serotonin after both applying the questionnaire and exposure to the craving-inducing film (P=0.001 and P=0.01 respectively). It is worth mentioning that none of the high-risk situations had any association with baseline serotonin level.

Table (1): Comparison between various levels of serotonin in different situations within patients:

Baseline 5 HT	5 HT after questionnaire	5 HT after film	Wilcoxon (Z)	P
39.31 ± 49.23	113.85 ± 144.49	-	-2.33	0.02*
39.31 ± 49.23	-	64.15 ± 80.15	-1.7	0.08
-	113.85 ± 144.49	64.15 ± 80.15	-2.23	0.02*

Significance: P<0.05

Table (2): Correlation between various 5 HT levels and clinical variables:

		Duration of abuse	Number of relapses
Baseline 5HT	r	-0.653	0.36
	p	0.04*	0.31
5 HT after questionnaire	r	0.611	0.76
	p	0.06	0.01*
5 HT after film	r	0.53	0.55
	p	0.12	0.1

Significance: P<0.05

Table (3): Confidence to Control Craving in the Different Situations Tested by the Craving Questionnaire

situations	**minimum**	**maximum**	**mean**	**Std.**
unpleasant emotions	16	76	51.0	22.02
physical discomfort	16	72	39.6	15.83
conflicts with others	20	76	49.2	18.77
pleasant emotions	16	76	47.4	21.58
urges/temptations	16	88	49.6	23.19
social pressure to use	12	74	42.6	20.46
testing personal control	24	84	51.6	23.88
pleasant times with others	12	72	41.6	22.33

Discussion

5HT and substance dependence:

This study showed that 5-HT levels were significantly lower in substance dependent patients compared to healthy controls. This finding is in accordance with previous research which suggests lowered 5 HT levels in substance dependence and considered it an etiological factor in the disorder. For example, ***Leyton et al. (2001)*** found that low 5-HT synthesis capacity in corticostriatal pathways may contribute to the development of impulsive behavior in persons with borderline personality disorder which is a common comorbid condition with substance dependence. An alternative explanation was presented by ***Deakin (2003)*** who hypothesed that projections of the anterior group of raphe 5HT cells (dorsal raphe nucleus) oppose the action of dopamine and mediate avoidance of threats and that impaired function sensitizes the dopamine system resulting in impulsivity and drug addiction. This also gets along with the finding that lowering of serotonin by rapid tryptophan depletion increases impulsiveness and decreases discrimination in normal individuals ***(Walderhaug, 2002).*** Conversely, other studies found that serotonin produced an inhibitory effect on drug intake (i.e., if you increased the serotonergic component, you make the drugs less attractive. However, now that we have better pharmacologic tools for studying serotonin neurotransmission we're finding a much more complicated picture. ***(Parsons, 2003).*** Interestingly, it was found that repeated administration of addictive drugs actually induces a decrease in the brain serotoninergic tone; thereby producing loss of self-control which characterizes drug craving in dependent subjects ***(Hamon, 2002).***

In a recent study testing effect of different drugs on delay aversion behavior (an aversion to waiting for rewards) in rats which positively correlates with aggression, substance abuse and persistence during extinction of conditioned responses suggesting a possible shared pharmacology, the results show that D(3)-receptor agonist 7-OH-DPAT slightly decreased choice for the large reward. Flesinoxan, 5-HT(1A)-receptor agonist, disrupted task execution by lowering choice for the large reward even at a delay of 0 s. Eltoprazine, 5HT(1A/1B)-receptor agonist, slightly increased choice for the large reward, but the 5-HT(1B)-antagonist GR127935 had no effect. Administration of D-cycloserine NMDA-receptor agonist, also had no effect on choice behavior. The data suggest the dopamine D(3)-receptor and the 5-HT(1B)-receptor are interesting targets for treating delay aversion impulsivity. These targets were correctly predicted by the positive correlation between delay aversion and aggressive behavior and the intimate links between delay aversion and substance abuse disorders ***(van den Bergh et al, 2006).*** Indeed, extensive neurobiological studies showed that the changes in central serotoninergic neurotransmission caused by cocaine and other addictive drugs are in fact opposite to those produced by drugs which enhance serotoninergic neurotransmission such as selective serotonin reuptake inhibitor. Accordingly, the latter effect very probably accounts for the capacity of these antidepressants to promote autoinhibition, and reduce both craving and consumption of drugs ***(Hamon, 2002).***

(5-HT) and craving:

In an attempt to localize areas of the brain responsible for craving and drug seeking behavior, scientists have been carrying a variety of research. Positron emission tomography was used to map regional cerebral blood flow (CBF) in 21 detoxified patients with alcohol dependence during exposure to alcoholic and non-alcoholic beverages. During the alcohol condition compared with the control condition, significantly increased CBF was found in the ventral putamen. Additionally, activated areas included insula, dorsolateral prefrontal cortex and cerebellum. Cerebral blood flow increase in these regions was related to self-reports of craving assessed in the alcoholic patients. It was thus concluded that cue-induced alcohol craving was associated with activation of brain regions particularly involved in brain reward mechanisms, memory and attentional processes ***(Olbritch et al, 2006).*** Another study measured brain activity in cocaine addicts and healthy subjects by functional magnetic resonance imaging (fMRI) while the subjects watched videotapes designed to elicit happy feelings, sad feelings, or the desire to use cocaine. The subjects indicated the onset of drug craving or emotional response, allowing comparison of groups before and after such feelings. Patients showed low activation of sensory areas during initial viewing of all videotapes, suggesting generalized alteration in neuroresponsiveness. Also cocaine cues lead to abnormally high cingulate and low frontal lobe activation in cocaine addicts. Addicts also show more general abnormalities in affect-related brain activation ***(Wexler et al, 2001).*** The development of novel pharmacological agents for the treatment of psychostimulant use disorders is an important research imperative. One potential target system that has been largely overlooked is the serotonin (5-HT) neurotransmitter system. In this study, we attempted to study 5HT levels and found a statistically significant difference between baseline 5HT and level after exposure to either visual or auditory cues with the patients reporting craving. Our results can be explained by preclinical studies that indicate that 5-HT2A R antagonists and/or 5-HT2C R agonists (presynaptic receptor) may effectively reduce craving and/or relapse, and likewise, enhance abstinence, while 5-HT2C R agonists may also effectively reduce cocaine intake in active cocaine users ***(Bubar & Cunningham 2006).*** Also our findings can be explained in light of Parsons conclusion who stated that when ethanol, cannabinoids, opioids, or psychostimulants are taken into body, serotonin levels in the brain are elevated significantly thereby playing a role in the motivation to continue taking drugs and that this may account for affective disorders similar to depression and anxiety often seen during withdrawal ***(Bardi, 2003).*** Interestingly, Parsons and his colleagues have subsequently found that serotonin-1B receptors enhance the reinforcing effects of amphetamine, alcohol, and opiates, and this effect does not seem to depend on route of consumption of the drug ***(Bardi, 2003)***. This goes with our finding of non significant difference in serotonin levels concidering route of opium intake.

It is worth mentioning that despite the agreement on the level of craving experienced subjectively on exposure to the craving-inducing film, yet it was found that serotonin increased markedly following applying the questionnaire than following

exposure to the craving-inducing film. This might be explained by the fact that when the patient is responding to the questionnaire, he/she is asked to think how they would be confident in response to these emotions, thoughts, or situation, this coincides with increased serotonin to face the craving thus multiple cognitive processes are involved for example memory, attention as well as activation of the reward system on a personalized level. However, as the film is not associated with expected response from the patient, so this actually represents what happens to the patient when suddenly developing craving and the elevation after the questionnaire might represent the neurobiological response in an attempt from the body to face craving and avoid relapse. Our results are not in agreement with a previous study comparing the effects of visual and auditory stimulation with that of cocaine (0, 5, 10, 20mg/kg; i.p.) on the extracellular serotonin (5-HT) activity in the occipital and temporal cortices in relation to behavior. Visual stimulation increased 5-HT in the occipital, but not temporal cortex, parallel to an increase in locomotion. Auditory stimulation decreased 5-HT in the auditory, but not occipital cortex, thus, showing a double dissociated 5-HT response. These data suggest that a locally restricted 5-HT response to sensory stimulation may gate behavioral activity sense-modality selectively. Cocaine affected 5-HT in the occipital cortex and behavioral activity in the same direction as visual stimulation, but in an amplified and prolonged way. In the temporal cortex cocaine also caused an increase in 5-HT. The findings demonstrate common effects of visual stimulation and cocaine on 5-HT activity in the occipital cortex in relation to locomotor activity ***(Maller et al, 2007).*** This study, thereby, suggests a stronger influence of visual cues than auditory cues in craving, an issue that needs further elaboration.

Serotonin over time of drug abuse

So, the balance between the facilitory and inhibitory mechanisms can be altered by long-term drug use. It was suggested that reduction in central serotonin leads to altered neuromodulation of the cortical and subcortical regions (e.g., orbitofrontal cortex, striatum and anterior temporal structures) that mediate important aspects of associative learning whereby exteroceptive stimuli acquire altered incentive motivational value. The brain serotonergic system plays a central role in the regulation of impulse-control mechanisms, and it is proposed that 5-HT deficiency may contribute to the loss of control over drug-taking, which is a crucial factor for the maintenance of addictive behaviour (**Ciccocioppo, 1999**). This explains the significant negative correlation found between baseline serum serotonin levels and duration of drug abuse rather than number of relapses which in some cases may be frequent but over a short period of time. Conversely, a significant positive correlation existed between serotonin level after exposure to auditory cues and number of relapses which may emphasize the strong role of the upsurge of 5 HT level during cue exposure and craving and consequently relapse.

Recommendations

The challenging components of drug addictions, including counteradaptation, sensitization, abstinence, craving and relapse need further neurobiological exploration and understanding, which may be done through

the use of advanced imaging and genetic techniques.

Hopefully, future studies will dissect out the influence of different serotonin receptor subtypes as well as different neurotransmitters involved in craving.

The studies focusing on understanding the mechanism of craving and relapse will set the groundwork for developing new therapeutics for drug addiction. As, on this basis, it can be suggested that the combination of selected serotonin receptor ligands with substance having the capacity to reduce the reinforcing appetitive properties of drugs of abuse (such as opioid receptor antagonist as naltrexone) might be a novel therapeutic approach of withdrawal in addicted subjects ***(Hamon, 2002)***

Limitations of the study

This study has put into consideration, the bias that can occur due to the differences in clinical heterogeneity of substance dependence by taking each patient as his/her own control.

Although, this study is the first to study the effect of craving from the neurobiological perspective in an Egyptian sample of substance use disorder patients, yet it had several limitations: First, the small sample size; Second, females in particular were underrepresented in that sample; Third, the results were obtained from an inpatient sample in a University hospital which represents a special subpopulation of substance use disorders with the most severe form of the disorder, so these results can't be generalized to the population of substance use disorder patients as a whole. Lastly, as subjects were inpatient they had no access to drugs (i.e., no drug expectancy which is a very important determinant of drug craving), this might have limited the severity of craving despite the fact that clinically being inpatient did not stop it altogether.

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Authors:

Haroun El Rasheed A.
Assiatant Prof. of Psychiatry
Institue of Psychiatry
Ain Shams University

El Sayed N.
Assiatant Prof. of Psychiatry
Institue of Psychiatry
Ain Shams University

Reda M.
Lecturer of Psychiatry
Institute of Postgraduate Childhood studies
Ain Shams University

Hussein H.

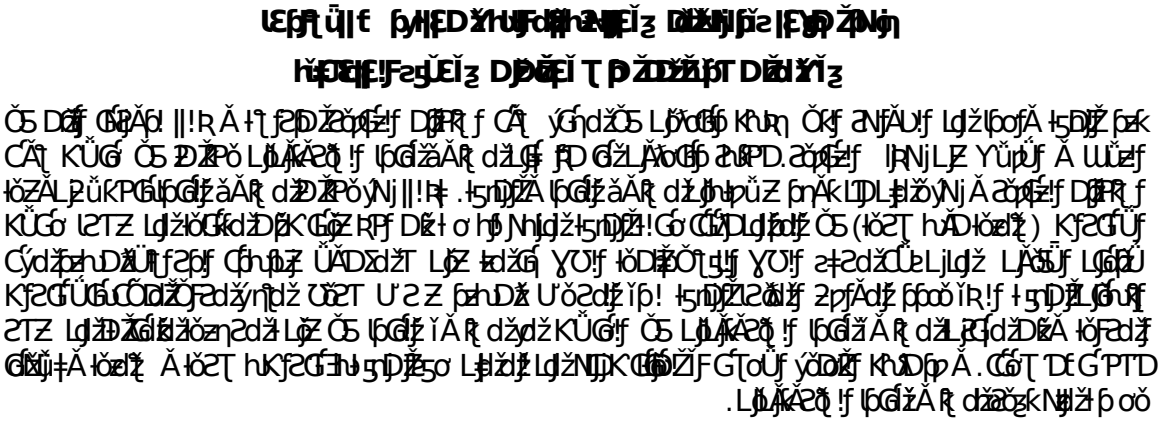
Lecturer of Psychiatry
Institue of Psychiatry
Ain Shams University

Abou Ghalia A.
Assistant Prof. of Biochemistry
Ain Shams University

Address of Correspondence:

Hussein H.

Lecturer of Psychiatry
Institue of Psychiatry
Ain Shams University



Structural Disconnectivity in Schizophrenia: Diffusion Tensor Imaging Study

Abdel-Azim Kh. and Ahmad Kh

The corpus callosum (CC) is the major white-matter tract that crosses the interhemispheric fissure in the human brain. It connects homologous regions of the cerebral cortex. Dysfunction of the corpus callosum can lead to deficits in sensory and cognitive integration. Magnetic resonance Diffusion Tensor Imaging (DTI) provides information about the microstructural organization of white matter integrity in vivo through measurement of directionality of motion of water molecules in the brain. The most commonly used index in DTI is "fractional anisotropy" (F.A.).The aim of this study is: to determine fraction anisotropy (F.A.) of genu and splenium of the corpus callosum in a sample of patients with schizophrenia and in control healthy individuals and to correlate clinical findings with F.A. in different parts of the corpus callosum within the patient group. We are testing the hypothesis of structural disconnectivity in schizophrenia using fractional anisotropy maps of corpus callosum. We found significant reductions of F.A. in genu and splenium in patient group compared to control group. We also found significant statistical correlations of F.A. with synonymous clinical symptoms in patients group reflecting degradation of myelinated fibers in the C.C. We conclude that DTI of water molecules within the human brain may provide valuable in vivo tool in examining the previously unknown clues to the microstructure of white-matter tracts in schizophrenia. Our findings suggest structural disconnectivity hypothesis of schizophrenia.

Introduction

In the last century, psychiatrists tried to define the neuropathology of schizophrenia through postmortem studies. Although histopathological characterization of schizophrenia proved to be elusive, identifiable neuropathological features were clearly and consistently associated with the illness. The findings of studies in the late nineteenth and early twentieth centuries were remarkably ambiguous in describing both diffuse and focal abnormalities in multiple brain structures (but failed actually to describe " single-lesion model "), which were subtle in magnitude and did not exactly explain the pathophysiology of schizophrenia nor different symptom-matology and hence the discovery of influential pharmacotherapy has been delayed.

Following this initial progress and with the advent of modern neuroimaging techniques, which enabled relatively non-invasive in vivo studies of brain structure and function, in the search for the neuropathology of schizophrenia, scientific discovery of the pathology of schizophrenia is meaningfully resumed. These techniques facilitate the emergence of different theoretical hypotheses of the illness. By virtue of these advanced neuroimaging methods, the new hypotheses of neuropathology of schizophrenia are now testable and could be elucidated.

More than 90 years ago, Bleuler (1911) proposed the term "schizophrenia" to describe a disease process that produces a *"splitting* of the psychic functions*"*. More recently, Friston KJ (1999) has renewed this concept and he described one of the most up-to-date hypotheses named *"disconnection syndrome"* models of schizophrenia.

These models draw on recent neuroscientific findings and highlight a lack of *"functional connectivity"* across multiple brain systems. These hypotheses could be tested over the past few years (Crespo-Facorro, et al., 1999; Andreas et al., 2001; Lee et al., 2003; Friston 2005 and Matthew et al., 2005). By aid of advanced neuroimaging techniques, the other face of the coin, *"structural connectivity hypothesis "*, has been emerged. One of the novels recently used in testing this hypothesis is Diffusion Tensor Imaging (D.T.I.) which is a new non-invasive structural imaging modality that measures the mobility of brain water molecules and the organization of fibers in white matter tracts in vivo (Basser et al, 1995).

Diffusion tensor imaging (DTI) provides information about the microstructural organization of deep tissues in vivo. Specifically, DTI provides information about white matter integrity through measurement of directionality of motion of water molecules in the brain. In the absence of barriers, water molecules in tissues undergo Brownian motion along all possible directions. This is referred to as "*isotropic diffusion"*. However, in the presence of barriers such as axonal membranes, myelin sheaths and microfilaments the diffusion of water molecules exhibits directional preference. This is referred to as "*anisotropic diffusion"*. Organized structures such as white matter fiber tracts exhibit a large anisotropy since the water diffusion is restricted along the length of the tracts rather than across them. A reduction in the anisotropy implies less restraint of water molecules that may be related to subtle white matter pathology and loss of integrity in fiber tracts that are not evident with other radiological modalities, including conventional MRI (Taber et al, 2002). The most commonly used index for quantifying the anisotropy is "*fractional anisotropy"* (F.A.) (deviation from pure *isotropic diffusion*), which varies from *zero* (diffusion equal in all directions) to *unity* (diffusion purely unidirectional). It has been recently shown to be rotationally invariant, provides excellent gray matter–to–white matter contrast, and has a high contrast to noise ratio than other measures (Hasan et al, 2004).

Any pathological factors (as oedema, demyelination or axonal loss) that alter the structural organization and / or reduce the density of axonal membranes [like acute cerebral ischemia (Huisman, 2003), multiple sclerosis (Ge et al., 2004), alcoholism (Pfefferbaum et al., 2004; 2005) and dementia (Sullivan et al., 2001; Head et al., 2004)] might be expected to cause a reduction in diffusion anisotropy values

compared with those measured in normal brain.

Thus, fractional anisotropy is taken to be a useful sensitive marker of neuronal integrity, with high fractional anisotropy values indicating healthy, intact white matter fiber tracts and is typically higher in fibers with a homogeneous or linear structure than in tissue with an inhomogeneous structure, such as areas with pathology (Lansberg et al., 2001) or crossing fibers (O'Sullivan et al, 2001; Pfefferbaum and Sullivan, 2003).

In white matter with relatively homogenous structure, such as the corpus callosum, the diffusion of the water molecules is restricted and bound in a structure with a primarily linear organization resulting in high F.A. (Pfefferbaum et al., 2003; Pfefferbaum and Sullivan, 2003).

Because D.T.I. may detect the pathology of white matter despite absence of macrostructural size variation measured with conventional neuroimaging techniques (like C.T.; M.R.I.; f.M.R.I. and M.R. Spectroscopy), so it may have the potential to identify structural correlates of impaired structural connectivity in schizophrenia.

The corpus callosum (CC) is the major white-matter tract that crosses the interhemispheric fissure in the human brain. It consists of approximately 200 million interhemispheric fibers, most of which connect homologous regions of the cerebral cortex (Biegon et al., 1994). Dysfunction of the corpus callosum can lead to deficits in sensory and cognitive integration (Yamauchi et al., 1997; Fabri et al., 2001and Pfefferbaum et al., 2003). Therefore, it has been a region of much interest in schizophrenia researches. Early post mortem studies indicated an increased thickness of the CC in patients, possibly reflecting a *"hyperconnection"* between the hemispheres as Rosenthal and Bigelow stated at 1972.

In vivo studies by using conventional neuroimaging techniques, neuroanatomic structural abnormalities and the morphology of the corpus callosum have been thoroughly investigated. Most investigators have studied callosal length and width (Nasrallah et al., 1986; Uematsu et al., 1988; Woodruff et al., 1995; Jacobsen et al., 1997), while few have investigated callosal shape (Casanova et al., 1990; DeQuardo et al., 1996). Volumetric methods are less sensitive to across subject variability (like sex differences and wide differences between whole brain volume) (Rauch and Jinkins, 1994; Jäncke et al., 1997) and less likely to capture subtle differences in anatomy between different groups of schizophrenic patients. Clinical and psychopathological heterogeneity in schizophrenic patients may also account for inconsistencies in results when assessing structural morphology, including morphology of the callosum. For example, patients with negative symptoms show smaller callosal sizes (Gunther et al., 1991; Woodruff et al., 1993), thicker callosa (Coger and Serafetinides, 1990) or no difference relative to other groups. Similarly, early-onset schizophrenic

patients have been shown to have larger total, anterior and posterior callosal areas compared to controls (Coger and Serafetinides, 1990; Jacobsen et al., 1997). As shown, the results have been inconclusive and controversial in proving the disconnection hypothesis of schizophrenia.

By using diffusion tensor imaging technique, our objectives in this study are: to determine fraction anisotropy (F.A.) of genu and splenium of the corpus callosum in a sample of patients with schizophrenia and in control healthy individuals and to correlate clinical findings with F.A. in different parts of the corpus callosum within the patient group.

We are testing the hypothesis of structural disconnectivity in schizophrenia using fractional anisotropy maps of corpus callosum.

Subjects and Methods

Twenty schizophrenic patients (12 males and 8 females; mean age 39.0±9.1 years; with mean duration of illness 12.0±7.3 years) and twenty normal controls (12 males and 8 females; mean age 39.9±8.1 years) were included in the study.

Patients were randomly recruited from outpatient services of Psychological Medicine Hospital in Kuwait. They were diagnosed by using the Structured Clinical Interview for Diagnostic and Statistical Manual (DSM-IV) criteria (First et al., 1996). We used the Arabic version (Al-Sammak A. and Mustafa A., 2001). Semi-structured sheet including socio-demographic data; past psychiatric, medical and surgical histories; family history and history of used neuroleptic medications was included. All patients were on antipsychotic medication (7 patients were on typical and 14 were on atypical antipsychotics at the time of the study). Psychiatric symptoms were assessed using the Brief psychiatric rating scale (BPRS) (Overall and Gorham 1962). Interviews verified absence of any current or past other Axis I diagnoses in those patients.

Healthy control subjects were recruited and selected to match the patient group for sex and age from the neuro-radiology department at Ibn Sina hospital -by one researcher- after completing the semi-structured sheet and the General Health Questionnaire (cut-off point = 7) (Goldberg 1972) and after exclusion of any past or current Axis-I psychiatric disorders or family history of psychiatric illness.

Exclusion criteria for both patients and controls included head trauma; drug abuse; hereditary neurological disorders; gross neurological or systemic disorders (evidenced by clinical and M.R.I. examinations); mental retardation and contraindication for M.R.I. All subjects gave informed written consent for their participation in this study after complete description of the procedure.

Corpus Callosum as a region of interest (ROI):-

The corpus callosum was the focus of this study, based on many factors. First, the corpus callosum is easily and reliably

identifiable on DTI images due to the large concentration of white matter fiber tracts. It is large enough for the ROI to be reliably placed with minimal intersubject variability in the directionality and spread of fiber tracts. This allows for a clear separation of white matter from gray matter and CSF, which are significant confounding factors in the DTI analysis. Second, corpus callosum white matter tracts are significantly influenced by cortical damage, thus subtle dysfunction of the prefrontal cortex or other brain regions by the effect of schizophrenia may be seen in changes in corpus callosum FA. Third، in order to compare regions of the corpus callosum and thereby examine fiber tracts connecting different cortical regions. Fourth, callosal pruning and myelination as well as interhemispheric coherence continue to develop into early adulthood, a factor that may be relevant to age of onset in schizophrenia (Njiokiktjien *et al.*, 1994). Lastly, callosal myelination begins prenatally and is susceptible to malnutrition, asphyxia and toxins of infectious origin; also, these same events are linked with aberrant neuro-developmental events in schizophrenia (Njiokiktjien et al., 1994).

Why Genu and Splenium?

Witelson (1989) divided C.C. into nine discriminated areas according to the connecting fibers passing through C.C. namely anterior genu (the most anterior area); middle genu; posterior genu; anterior body; posterior body; isthmus; anterior splenium; middle splenium and posterior splenium (the most anterior area). Anterior genu contains the connecting fibres of prefrontal cortices. While, middle splenium contains the fibers connecting superior and inferior temporal gyri together. Other areas of the C.C. contains fibers connecting premotor; precentral; post-central; posterior parietal and occipital areas on both hemispheres respectively (anteriorly to posteriorly).

Many recent studies have demonstrated abnormal brain structure and function in the frontal and temporal lobes of patients with schizophrenia. Functional imaging and D.T.I. studies show abnormal frontotemporal activations on various neuropsychological tasks lending support to the hypothesis that the core feature of schizophrenia is a disruption of fronto-temporal structural disconnectivity (Honey et al, 2002 and Burns et al., 2003). Hence, we chose anterior genu and middle splenium as R.O.Is because they contain the fibers which are convenient to test our hypothesis and because they are the most widened areas of the C.C. so can be described easily through axial images.

Why axial plane?

We obtained the anisotropy images in the axial plane rather than in the sagittal plane, with multiple sections through the corpus callosum. We believe that this approach results in more representative images of the entire corpus callosum than the acquisition of a single mid-sagittal image.

M.R. Imaging data acquisition and analysis

DTI was performed with a 1.5 Tesla scanner (Signa; GE, medical system, Milwaukee, Wis) by using 8 Channel head Coil, landmark to the nasion and pad the patient to reduce the likelihood of artifacts related to motion. The diffusion tensor MR imaging protocol consisted of 3-plane localizer series and ASSET calibration scan taking into consideration that the entire brain anatomy included in the ASSET calibration scan. Optimization of TE to ensure that the lowest TE possible is utilized base on the gradient amplitude applied (B-Value). Single-shot spin- echo echo-planar sequence with ASSET series in axial plane using the following parameters Time to repeat (TR) was 6200msec, Time to echo (TE) was 111msec. Diffusion sensitization gradient encoding was applied in 25 directions by using B-Value 1000sec/mm2. A total 25 diffusion weighted images were obtained for each image section, and images through the whole brain were obtained. The slice thickness was 5mm with no intersection gap, the matrix size was 128 X 128 and Field of view was 24X24 cm2. The imaging time for the diffusion tensor MR sequence was approximately 2 minutes. In addition to diffusion tensor MR sequence, conventional MR imaging sequence was performed to exclude white matter lesions. Axial FSE T2 weighted sequences with the following parameters Time to repeat (TR) 700msec, Time to echo (TE) 88msec, Matrix size 512X512, FOV 24X24cm2 with slice thickness 5mm and intersection gap 1.5mm.

Image analysis

The raw diffusion tensor data were transferred to an independent workstation (Advantage Windows; GE Medical Systems) and processed with a computer software program (Functool; GE Medical Systems) to get index of anisotropy, we chose to use fractional anisotropy (FA). FA represents the anisotropic portion of total diffusion. To get FA, A uniform ovoid regions of interest (ROIs) were placed by using the functool software. All ROIs used in this study were manually placed by one neuroradiologist who was blinded to the patients' characteristics. The ROIs were drawn in mid part of genu and splenium on the section showing maximum thickness; it was at least 70 mm2. Slices contiguous with the one selected were examined to avoid the partial volume effects of cerebrospinal fluid (CSF) fig (1 and 2).

The FA value is unitless because it represents a ratio of diffusion coefficients. The calculations for FA were performed for each voxel and displayed as an anisotropy map, which was appropriately scaled for display.

Statistical Analysis

Data were collected and coded then entered into an IBM compatible computer, using the SPSS version 12 for Windows. Entered data were checked for accuracy then for normality, using Kolmogorov-Smirnov and Shapiro-Wilk tests, and proved to be normally distributed. Qualitative variables

were expressed as number and percentage while quantitative variables were expressed as median, mean ($\overline{X}$) and standard deviation (S).

The arithmetic mean ($\overline{X}$) was used as a measure of central tendency, while the standard deviation (S) was used as a measure of dispersion.

The following statistical tests were used:-

1-Independent samples t-test was used as a parametric test of significance for comparison between two sample means, after performing the Levene's test for equality of variances.

2-The χ^2-test (or likelihood ratio =LLR) was used as a non-parametric test of significance for comparison between the distribution of two qualitative variables.

3-The Spearman's rank correlation coefficient (r) was used as a non-parametric measure of the mutual relationship between two not-normally distributed quantitative or ordinal variables.

A 5% level is chosen as a level of significance in all statistical significance tests used.

Results

There was no significant difference between patients and their matched healthy control subjects regarding age and gender differences ($p > 0.05$). 70% of patients were currently single or divorced compared to only 20% of the control group (Likelihood Ratio = 16.9 and $p=0.001$). 40% and 10% of the patients finished only primary and preparatory schools respectively compared to 40% and 35% of the controls who finished secondary schools or graduated from the university respectively (Likelihood Ratio = 26.8 and $p=0.000$). Also, 70% of patients were currently unemployed or retired compared to 60% of the controls who were working currently at senior level works (Likelihood Ratio = 22.9 and $p=0.000$).

Fractional Anisotropy of the corpus callosum

By comparing Fractional Anisotropy (F.A.) in both the genu and splenium of the corpus callosum in both groups using t-test, we found that , F.A. of genu in schizophrenia group (0.552 ± 0.119) was significantly less than F.A. in controls (0.641 ± 0.075) (t = 2.8 and $p=0.008$) and that F.A. of splenium in schizophrenia group (0.596 ± 0.102) was significantly less than F.A. in controls (0.778 ± 0.030) (t = 7.9 and $p=0.000$)(Figure 3).

Table (2) demonstrates the correlation between F.A. (in both genu and splenium) with duration of illness; total score of Brief Psychiatric Rating Scale (B.P.R.S.) and subscores of items of B.P.R.S. in patients group. No significant correlations were found between all of these variables ($p > 0.05$).

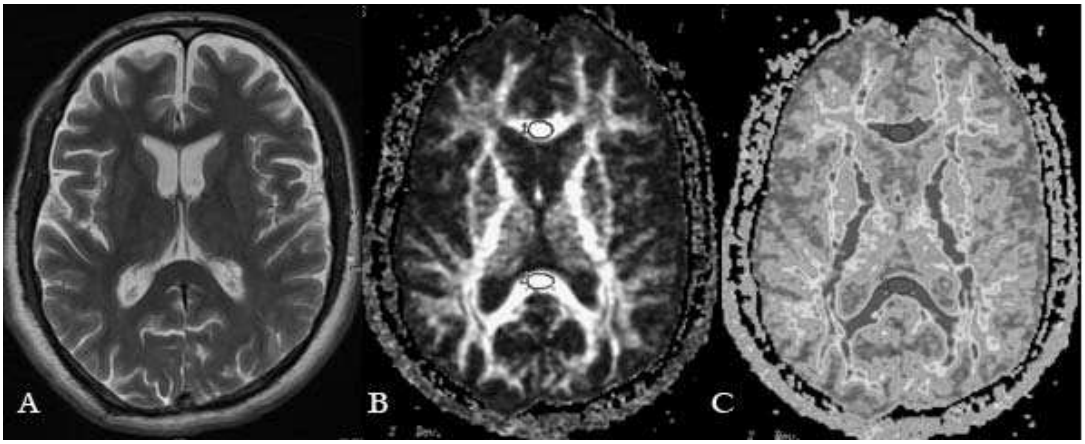


Figure (1): Normal control subject Male 39ys. old; (A) Ax T2w image at the level showing maximum thickness of corpus callosum at genu anterior and splenium posterior, (BandC) are fractional anisotropy maps (FA maps) in gray (A) and colour (B) scales where white matter is white and red in the coloured image ROI is seen placed at mid part of genu and splenium measuring FA values.

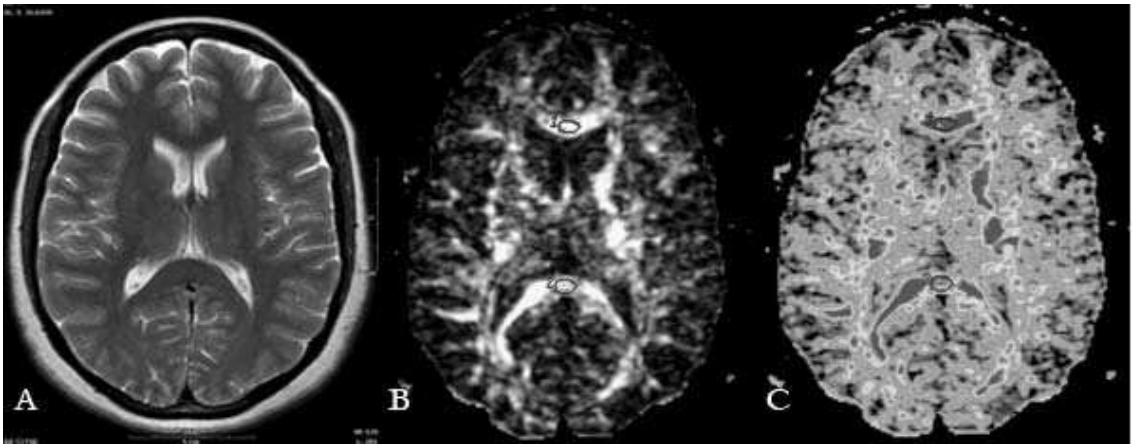


Figure (2): Male 37ys. old patient with schizophrenia; (A) Ax T2w image at the level showing maximum thickness of corpus callosum at genu anterior and splenium posterior and no abnormality, (BandC) are fractional anisotropy maps (FA maps) in gray (A) and colour (B) scales showing the thinned out white matter tracts and the ROI seen at mid part genu and splenium measure the FA values.

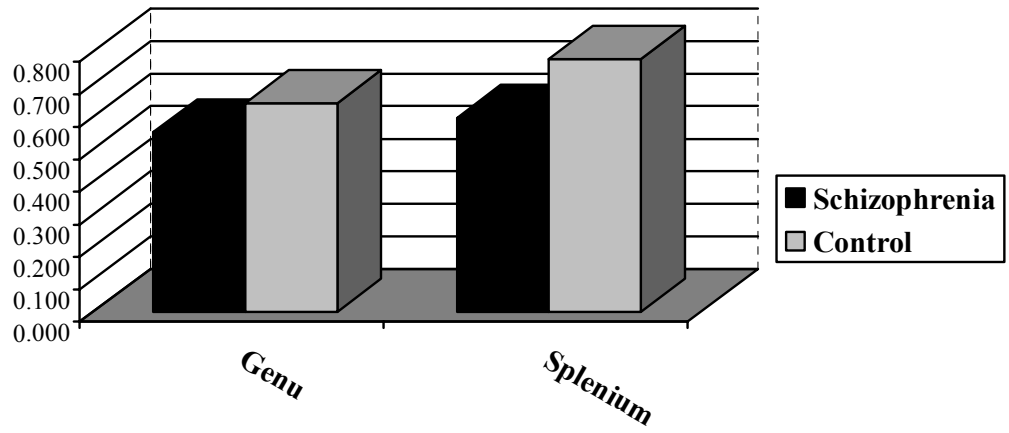


Figure (3): Comparison between F.A.* in genu and splenium in both groups

* F.A. = Fractional Anisotropy (dimensionless units)

Correlating F.A. with age and gender differences in both groups

Using Spearman's rho test, there were no significant statistical correlations between age and F.A. of genu or splenium in both studied groups ($p > 0.05$). As shown in table (1), there were no significant statistical differences between males and females of each group regarding F.A. in genu and splenium ($p > 0.05$).

Table (1):- Correlation between gender and F.A. in genu and splenium in each group

F.A.	Schizophrenia group				Control group			
	Male (n=12)	Female (n=8)	t	*p*	Male (n=12)	Female (n=8)	t	*p*
Genu	0.546 ± 0.139	0.568 ± 0.364	.44	*0.67*	0.653 ± 0.074	0.613 ± 0.069	1.23	*0.23*
Splenium	0.578 ± 0.114	0.596 ± 0.070	.40	*.69*	0.772 ± 0.026	0.745 ± 0.030	1.52	*0.19*

F.A. = Fractional Anisotropy (dimensionless units)

t = t-value (Independent sample t-test)

Correlation is significant at the 0.05 level (p value)

Correlating F.A. with clinical findings in patient group

Table (2):- Correlation between genu and splenium F.A. with clinical findings

Clinical variables	Genu F.A.		Splenium F.A.	
	r	*p*	r	*p*
Duration of illness(years)	0.583	0.57	0.230	0.82
B.P.R.S. score	0.168	0.48	0.076	0.75
Conceptual disorganization	0.733	0.000 **	0.218	0.36
Hostility	0.580	0.02 *	0.804	0.000 **
Suspiciousness	0.696	0.01 *	0.777	0.000 **
Hallucinatory behaviour	0.624	0.003 *	0.700	0.002 *
Emotional withdrawal	- 0.631	0.003 *	- 0.429	0.09
Blunted affect	- 0.566	0.009 *	- 0.393	0.19
Motor retardation	- 0.620	0.004 *	- 0.369	0.06
Anxiety	0.291	0.21	0.582	0.02 *
Unusual thought content	0.706	0.001 **	0.242	0.30

F.A. = Fractional Anisotropy (dimensionless units)

r = r-value (Spearman's rho test)

* Correlation is significant at the 0.05 level (p value)

* * Correlation is significant at the 0.05 level (p value)

(-) = Negative correlation

N.B.:- Other symptoms of B.P.R.S. not included in the table, were found to have statistical insignificance when correlated with F.A.

By correlating all items of B.P.R.S. with F.A. in genu and splenium, the most evident significant correlations were as follows:-

- Out of 16 items of B.P.R.S. have significant correlations with genu F.A. The highest significance was for conceptual disorganization and unusual thought content.
- Only 4 items of B.P.R.S. showed significance when correlated to splenium F.A. The highest significance was for hostility and suspiciousness.
- Scores of emotional withdrawal; blunted affect and motor retardation had the only negative correlations with F.A. in both of genu and splenium.

Discussion

The present study examined whether there are regionally C.C. abnormalities in patients with schizophrenia compared to control subjects, and whether schizophrenia results in an aberration in age; gender or duration of illness related alterations in C.C. We applied current analysis techniques to fractional anisotropy maps obtained from D.T.I. data to test the hypothesis that these specific white matter tracts of C.C. would be disrupted in patients with schizophrenia due to structural disconnectivity of the illness. Such a disruption would manifest itself as a reduction in fractional anisotropy values in patients with schizophrenia compared with controls.

We found a statistical significant reduction of F.A. in genu of schizophrenic group compared to control group ($p = 0.008$) and a high significant statistical reduction of splenium of schizophrenic group compared to control group ($p= 0.000$). Our results are in agreement with previous researches which found the same reduction in F.A. in schizophrenia group in both the genu and splenium (Lim et al., 1999; Agartz et al., 2001 and Price et al., 2006). Others found the significant difference in patients with schizophrenia only in the genu (Kitamura et al., 2005 and Buchsbaum 2006) or only in the splenium (Foong et al., 2000 and Mitelman et al., 2006). While, other researchers did not find any statistical difference between F.A. in both groups (Steel et al., 2001 and Foong et al., 2002). Different methods in measuring F.A.; patient populations and difference in the numbers of the studied cases may explain these differences.

Our findings about the reduction in F.A. in the genu and the splenium suggest a disruption of axonal integrity likely to be related to the density or organization of fibers. It is possible that DTI changes may also reflect myelin abnormalities. However, Miranda et al., (1998) demonstrated similar F.A. values in partially myelinated or unmyelinated white matter structures in the infant brain compared with the fully myelinated adult brain indicating that the contribution of myelin abnormalities to changes in anisotropy may be less significant than that from axonal abnormalities.

From the results, it is evident that F.A. is less in genu than in splenium in both of the schizophrenia and control groups. The explanation for this finding may lie in the regional differences of the microscopic structure of the corpus callosum that are due to regional variations in normal development or regional variations in age-related effects. This finding may be an important clue regarding the organization of the corpus callosum, and it may help to explain the behavior of the corpus callosum in schizophrenia. Neeraj et al., (2002) conducted a D.T.I. study in forty two healthy individuals and they found the average values of the F.A. for the genu, body, and splenium of the corpus callosum were 0.400, 0.456, and 0.539, respectively. The differences between these values are statistically significant ($P < .01$). They

proposed that these anisotropic variations in the corpus callosum may be due to a combination of the following physical and geometric factors in splenium: 1) tighter packing of axons, 2) less permeable myelin sheaths, 3) fewer obliquely oriented axons, 4) altered radius of individual axons, and 5) the presence (or absence) of structures other than myelin sheaths within the splenium that restrict water diffusion as collagenous fibers.

Our finding regarding gender ; age; type of antipsychotics mainly used (typical or atypical) and duration of illness and their correlations to F.A. failed to predict the DTI changes in schizophrenic patients and in control group suggesting that these abnormalities are unlikely to be progressive although this would need to be confirmed by longitudinal studies. These findings may be due to the relatively small number of our sample. The same results were found also by Price et al., (2005).

By correlating the clinical findings of the patients (total score of Brief Psychiatric Rating Scale -B.P.R.S.- and subscores of the sixteen items of B.P.R.S.) with F.A. in both the genu and splenium to specify which symptoms are correlated significantly more to the genu and / or splenium. We found 8 and 4 symptoms out of 16 were significantly correlated to F.A. for the genu and splenium respectively (as shown in table 2). Other symptoms did not reach the statistical level of significance ($p > 0.05$). The most significant correlations for the genu were conceptual disorganization and unusual thought content and for the splenium were hostility and suspiciousness. It is to be noted that the main negative symptoms of B.P.R.S. namely blunted affect; emotional withdrawal and motor retardation were negatively correlated to F.A. in both the genu and splenium, reaching the significance level only for the genu.

It is well evidenced now that the main function of corpus callosum is to organize the transfer of information between the two homologous hemispheres. Anterior genu is responsible for connecting both prefrontal cortices involved in higher-order processing of motor control, planning, cognitive and executive functions. Lesions in prefrontal areas lead to some symptoms as change in personality; loss of inhibitions; poor judgment; apathy; indifference and poor abstraction. Body and isthmus of C.C. connects premotor; precentral; postcentral and posterior parietal areas on both sides of the brain. They are involved mainly in motor and sensory functions; cortical inhibitions of bladder and bowel; language and other skills like calculation and construction. While middle splenium connects bilateral temporal gyri (including the limbic system) which are involved in memory; learning and emotions (Lindsay et al., 1997).

So, the results of our study can be explained by either of two points of view. Firstly, Thomalla et al., (2004) found reduced F.A. in the anterior regions of C.C. in cocaine-dependant subjects and he supposed that this reduction is due to damage in prefrontal cortex. Their hypothesis is supported by an

earlier post mortem study which showed that the anterior corpus callosum exhibits Wallerian degeneration after injury to the inferior frontal and anterior inferior parietal regions of the brain (De Lacoste et al, 1985). So the degeneration of the white matter tracts is secondary to the cortical pathology. Following this hypothesis in interpretation of our results is less plausible because it necessitates the presence of bilateral pathology in many lobes of the brain at the same time to explain different symptomatology of schizophrenia group.

Second explanation is more powerful and instructive. Reduced F.A. in genu and splenium is due to reduced function ("hypoconnectivity" or "disconnection hypothesis") of the corpus callosum itself rather than damage to the prefrontal and temporal cortices. This hypothesis is supported by many histopathological studies which found the numbers of axonal fibers connecting the cortical regions across the C.C. to be smaller in schizophrenia which disrupt the connection in the cortical neurons or axons in focal areas in C.C. (Nasrallah et al., 1983; Casanova et al., 1989; Friston et al., 1998 and Diwadkar et al., 2001).

Other studies suggested region specific differences in fiber composition of C.C. association higher cortical regions (as prefrontal and temporal cortices) project via small axons (<2 mm in diameter) to the genu and splenium respectively. These axons found to be affected mainly in schizophrenia and lead to reduced F.A., while other visual; somatosensory; primary motor and sensory cortices project via large axons (>2 mm) to other areas of C.C. (Aboitz et al., 1992a and1992b). Hence, significant correlations between some symptoms as conceptual disorganization; unusual thought content; blunted affect; motor retardation and emotional withdrawal and other symptoms as hostility; suspiciousness and anxiety in our schizophrenic sample with F.A. of genu and splenium respectively are convenient.

It remains possible that DTI abnormalities may have been present in other regions of the corpus callosum and in other areas mainly prefrontal and temporal white matter in the brain which need more sophisticated techniques. Therefore, our findings in this study suggest the structural disconnectivity hypothesis in schizophrenia but certainly do not exclude the possibility of abnormalities in other regions of white matter.

Conclusion

DTI of water molecules within the human brain may provide valuable in vivo tool in examining the previously unknown clues to the microstructure of white-matter tracts in schizophrenia. The significant reductions of F.A. in genu and splenium of the C.C. and the statistical correlations of F.A. with synonymous clinical symptoms in patients group reflect degradation of myelinated fibers in the C.C. and suggest structural disconnectivity hypothesis of schizophrenia.

Limitation of the study

However, there are some methodological limitations in this study:

1- Relatively small number of patients.

2- F.A. was assessed only in genu and splenium of the C.C. No other areas of the white matter were studied.

Future researches

1- To study the connectivity hypothesis in schizophrenia by using more advanced techniques like tractography and the planar model which describes the spread of heterogeneous fibers in term of planar architecture other than uniaxial model.

2- D.T.I. of other white matter tracts as arcuate fasciculus; uncinate fasciculus; U shaped fibers; longitudinal fascicule; cingulated fascicule and long associative fibers will throw more light on the nature of connection pathology in schizophrenia.

3- Combining DTI with neuro-physiological tests of inter-hemispheric processing.

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الـدليل التشخيصـي والإحصـائي الرابـع للاضـطرابات النفسية_ المعايير التشخيصية، الرابطية الأمريكية للطب النفسي، ترجمة د. أمينة السماك، مدرس علم النفس، كلية العلوم الاجتماعية، الكويت، ود. عادل مصطفى محمد اخصائي الأمراض النفسية، مستشفى الطب النفسي ، الكويت،مكتبة المنار الإسلامية، الكويت،(٢٠٠١) .

Authors:

Abdel-Azim: Kh
Lecturer of Psychiatry,
Faculty of Medicine
Ain Shams University

Ahmad:Kh
Lecturer of Radiology
Faculty of Medicine
Ain Shams University, Cairo.
e-mail: dr_khaled68@hotmail.com

Address of Correspondence:

Abdel-Azim: Kh
Lecturer of Psychiatry,
Faculty of Medicine
Ain Shams University

e-mail: khaledazima@msn.com

Assessment of cognitive functions after coronary artery bypass grafting and its relation to cerebral blood flow

El-Batrawy A., Hazzou A., Mostafa M. and Reda W.

Abstract

Background: It is widely assumed that decline in cognition after coronary artery bypass grafting (CABG) is related to use of the cardiopulmonary bypass pump. Because most studies have not included comparable control groups, it remains unclear whether postoperative cognitive changes are specific to cardiopulmonary bypass, general aspects of surgery, or vascular pathologies of the aging brain. Methodology: A prospective study was done on 30 patients undergoing CABG and 18 heart healthy controls. Patients were evaluated at baseline (preoperatively), 1 month and 3 months after the operation by Wechsler intelligence scale, Wechsler memory scale and transcranial Doppler. Results: the patient group showed cognitive decline at 1 month followed by return to near baseline values at 3 months. This decline was related to decreased cerebral blood flow during the operation. Conclusion: Neurocognitive dysfunction is a frequently occurring complication of coronary artery bypass grafting. The etiologic contribution of cardiopulmonary bypass to this complication will remain unclear until a randomized trial that directly compares off-pump and on-pump bypass surgery is carried out.

Introduction

Coronary artery bypass grafting (CABG) with the use of cardiopulmonary bypass (CPB) is associated with significant cerebral morbidity. The two main clinical manifestations of brain injury after CABG are stroke and cognitive decline (Roach et al. 1996). Cognitive sequelae after coronary artery bypass grafting (CABG) have been the focus of research interest for several decades. As a review study by Mahanna et al. in 1996 has shown, the reported incidence of morbidity varies; incidence of inhospital postoperative neuropsychological impairment as high as 79% has been cited. The discrepancy in results is very likely multifactorial and can be explained by heterogeneous definitions of cognitive decline and differences in neuropsychological test instruments, practice effects, testing intervals, surgical technique, and others. The assessment of cognition before and after cardiac operation is now used extensively as a measure of surgical outcome, after reports a decade ago that suggested "intellectual dysfunction" could affect as many as 80% of patients (Shaw et al. 1986, Newman et al. 1987). The incidence of cognitive decline after cardiac operation has been subsequently used to compare outcomes in different centers, to assess the efficacy of neuroprotective drugs, and to improve perfusion techniques and surgical management (Patel et al. 1996, Murkin 1993).

The precise pathophysiologic features of cognitive impairment are not certain but have been attributed to the microembolic, inflammatory, and nonphysiologic perfusion factors associated with cardiopulmonary bypass (CPB) (Benedict 1994). Cognitive impairment also occurs after noncardiac operations but is reported to be more frequent and severe after cardiac

operation with CPB. Although cognitive impairment after noncardiac operation is explained by patient-related factors (eg, advanced age, ill health), impairment that occurs after cardiac operation is invariably attributed to CPB (Smith 1988, Hammeke and Hastings 1988, Vingerhoets et al. 1997). The feasibility of the performance of certain coronary grafts without CPB has recently been established. It has been postulated, but not proved, that avoidance of CPB may reduce the postoperative morbidity associated with extracorporeal circulation. Specifically, it is suggested that coronary artery bypass grafting (CABG) without CPB should minimize postoperative cognitive impairment (Treasure et al. 1989).

At a consensus meeting in 1994, several guidelines for the assessment of neuropsychologic deficits after CPB were established. It was recommended that the neurologic and neuropsychologic state be assessed before the operation to provide accurate baseline information. A second important recommendation was that the analysis should be based on the individual change in performance from baseline to a particular time after the operation. In general, practice effects cause the overall group performance to improve after the operation. Accordingly, when the overall postoperative mean is compared with the preoperative mean, the decline of some individuals is overshadowed by the improvement of others. Also, it was agreed that a late assessment (ideally after 3 months) should be included in the study design, because the patients' performances are unstable in the immediate postoperative period (Murkin et al. 1995).

It remains unclear whether changes in cognitive performance after open-heart surgery are specifically related to the use of cardiopulmonary bypass (CPB), to more general aspects of surgery such as type and duration of anesthesia, and type and duration of surgery or to underlying pathologies related to the aging brain such as cerebrovascular disease. To answer these questions we studied the effect of extracorporeal circulation on the cognitive functions of the brain in CABG surgery.

Methods

A case control study was carried out using data collected from 30 patients undergoing first-time CABG by a single surgeon and 18 heart healthy controls. All data were collected prospectively at the time of operation, 1 month, and 3 months after the operation. Cases were defined as patients who underwent the CABG and controls were defined as all other voluntary participants.

A written informed consent was obtained from all participants who took part in the study. Patients with previous neurological or psychiatric illness were excluded by taking detailed and full neuropsychiatric history and carrying on the general health questionnaire. The control group was screened for the following medical history variables: diabetes mellitus, kidney disease, hypertension, coronary artery disease (including myocardial infarction, angina, high cholesterol), stroke/TIA, peripheral vascular disease, and medications used to treat the above conditions. The controls were selected to be comparable with the patient group in terms of age and sex.

The preoperative assessment included all of the usual clinical and investigational measures and a detailed general level of risk was expressed to the patients. Full neurological assessment with special

emphasis on information on previous neurological events was done including a detailed neurological examination according to the National Institutes of Health Stroke Scale (NIHSS) (Brott et al. 1989) was carried on the day before the surgery.

The baseline neuropsychological assessment was carried out on the day before the operation and consisted of Wechsler Intelligence Scale (WAIS) and Wechsler Memory Scale (WMS). These are accepted tests of global cognitive function assessment. The tests were presented in a fixed order according to conventional practice and the scores were arranged so that higher scores indicated better neuropsychologic performance. In addition because cognitive functions may be affected by mood, each patient's current mental health was also assessed by means of the Hamilton Depression Scale (HDS).

The patients were also assessed neurologically, in addition to the history and neurological examination, by using Transcranial Doppler ultrasound (TCD) to measure the changes in mean flow velocity (MFV) of the cerebral vessels. We used the TCD MDX- TCD-7 software (version 7.3) apparatus multi-channel Doppler operating at 2 MHz. Insonation of the middle cerebral artery (MCA) on both sides through transtemporal window. MCA blood flow velocity was recorded bilaterally with TCD. Transducers were immobilized throughout the operations with a head ring. Measures of cerebral perfusion were recorded manually for each side at 15-minutes intervals during the operation for each patient. And the readings were summed and their mean was calculated for the 3 different phases (before anesthesia, during anesthesia and during on-pump period).

General anesthesia was induced in all patients of the study by Midazolam 2-5 mg, Fentanyl 150-250 mcg and propofol 30-50 and maintained by Sevofluarane inhalational anesthetic. Cistracrium was used as skeletal muscle relaxant in all patients given at top-up dose every 45 minutes in a dose of 0.3 mg/kg.

Standard surgical technique was used in all patients. Normothermic cardiopulmonary bypass (CPB) was instituted and maintained using ascending aortic cannulation and two-stage venous cannulation of the right atrium after palpation of the ascending aorta to avoid the calcified segments. Myocardial protection was achieved with intermittent antegrade hyperkalemic warm blood cardioplegia.

During cardiopulmonary bypass, pump flow was maintained between 2.0 and 2.5 L/minute per square meter and mean arterial pressure between 50 and 60 mm Hg. Norepinephrine was used as needed to maintain the mean arterial pressure at the above mentioned values.

Both neuropsychological assessments and TCD were repeated after one month and 3 months postoperatively to assess if there is cognitive decline and affection of cerebral blood flow after on-pump CABG which is the main aim of our study.

Statistical analysis

Statistical analysis was carried out with SPSS 10.0 software. Continuous variables are presented as mean and standard deviation. Comparisons between patients and controls were evaluated by t test. Statistical significance was associated with a p value of less than 0.05.

Results

In this study we investigated 30 patients undergoing CABG surgery, 18 (60%) males and 12 (40%) females with mean age of 54.1 ± 10.8. Of these, 50% (n=15) had diabetes mellitus, 60% (n=18) had hypertension and 30% (n=9) were smokers.

The control group was 18 individuals, 9 (50%) males and 9 (50%) females with mean age of 53.3 ± 8.2. 50% (n=9) had diabetes mellitus, 66.7% (n=12) had hypertension and 33.3% (n=6) were smokers.

Results of TCD mean flow velocity (MFV), Wechsler intelligence scale and Wechsler memory scale preoperative and 1 month and 3 months postoperative consecutively are shown in tables 1, 2 and 3.

When comparing MCA MFV before anesthesia, during anesthesia and during on-pump period, we found that during anesthesia the MCA MFV decreased significantly on both sides then it was increased again significantly during the on-pump time (Table 4).

Direct relation between cognitive functions and the lt. MCA mean flow velocity was found during anesthesia but not during on-pump period. This relation was not found with rt. MCA (Table 5). Figure 1 shows sample of TCD of MCA before anesthesia, during anesthesia and during on-pump period.

Table 1: Results of MCA mean flow velocity (MFV), Wechsler intelligence scale and Wechsler memory scale preoperatively.

	Control	Patients	p value
Number	18	30	
Age	53.3 ± 8.2	54.1 ± 10.8	0.797
Rt. MCA MFV	71 ± 10.3	74.5 ± 19.3	0.418
Lt. MCA MFV	74.5 ± 5.4	69.4 ± 15.2	0.105
Verbal IQ	99.8 ± 5	100.9 ± 17.9	0.761
Performance IQ	99.5 ± 2.8	96.7 ± 15.1	0.331
Total IQ	100.5 ± 3.9	96.5 ± 16.7	0.219
PINF	5.66 ± 0.4	5 ± 1	0.004*
Orientation	5 ± 0	4.7 ± 0.4	0.001*
Memory control	6 ± 0	3.3 ± 2.2	< 0.001*
Immediate recall	11.5 ± 0.5	6.2 ± 2.9	< 0.001*
Memory span	10.5 ± 0.5	7.6 ± 1.9	< 0.001*
Visual reproduction	9.5 ± 0.5	3.4 ± 2.8	< 0.001*
Paired associated learning	11.3 ± 2.5	7.8 ± 4.9	0.002*
Total memory score	113 ± 3.7	78 ± 17.8	< 0.001*
Total HDRS	3.5 ± 0.9	11.5 ± 7.5	< 0.001*

HDRS: Hamilton Depression Rating Scale, IQ: Intelligent Quotient, Lt.: Left, Rt.: Right, MCA: Middle cerebral artery, MFV: Mean flow velocity, PINF: Personal and current information. * $p < 0.05$-- significant

Table 2: Results of MCA mean flow velocity (MFV), Wechsler intelligence scale and Wechsler memory scale 1 month postoperative.

	Control	Patients	p value
Rt. MCA MFV	71.3 ± 9.1	77.5 ± 18.8	0.136
Lt. MCA MFV	73 ± 7.3	71.9 ± 18.1	0.776
Verbal IQ	103 ± 4.5	95.4 ± 19.7	0.2
Performance IQ	99 ± 3	92.7 ± 15.3	0.037*
Total IQ	100.5 ± 4	91.6 ± 17.6	0.012*
PINF	5.66 ± 0.4	5.2 ± 0.6	0.008*
Orientation	5 ± 0	4.4 ± 0.8	< 0.001*
Memory control	6 ± 0	3.2 ± 1.6	< 0.001*
Immediate recall	11.6 ± 0.4	7.2 ± 2.4	< 0.001*
Memory span	10.3 ± 0.48	7.3 ± 1.87	< 0.001*
Visual reproduction	9.33 ± 0.4	2.5 ± 2.3	< 0.001*
Paired associated learning	11.5 ± 1.6	5.4 ± 3.3	< 0.001*
Total memory score	114.1 ± 2.8	73.9 ± 13.5	< 0.001*
Total HDRS	3.1 ± 0.7	14.8 ± 7.4	< 0.001*

HDRS: Hamilton Depression Rating Scale, IQ: Intelligent Quotient, Lt.: Left, Rt.: Right, MCA: Middle cerebral artery, MFV: Mean flow velocity, PINF: Personal and current information. * p < 0.05-- significant

Table 3: Results of MCA mean flow velocity (MFV), Wechsler intelligence scale and Wechsler memory scale 3 months postoperative.

	Control	Patients	p value
Rt. MCA MFV	71.3 ± 9.5	81.1 ± 16.7	0.013*
Lt. MCA MFV	72.8 ± 8	71.9 ± 14.5	0.776
Verbal IQ	100.8 ± 4.2	101.6 ± 18.25	0.827
Performance IQ	100.3 ± 2.8	97.2 ± 15	0.278
Total IQ	101.1 ± 3.9	97.1 ± 16.9	0.217
PINF	5.5 ± 0.5	5.3 ± 0.6	0.246
Orientation	4.8 ± 0.3	4.9 ± 0.3	0.5
Memory control	5.8 ± 0.38	4.2 ± 1.7	< 0.001*
Immediate recall	11.1 ± 0.3	6.9 ± 2.3	< 0.001*
Memory span	10.6 ± 0.4	7.9 ± 1.6	< 0.001*
Visual reproduction	9.6 ± 0.4	4 ± 2.4	< 0.001*
Paired associated learning	12.3 ± 2.1	8.3 ± 4.5	< 0.001*
Total memory score	114.5 ± 2.5	80.2 ± 16.7	< 0.001*
Total HDRS	3 ± 0.5	6.9 ± 2.2	< 0.001*

HDRS: Hamilton Depression Rating Scale, IQ: Intelligent Quotient, Lt.: Left, Rt.: Right, MCA: Middle cerebral artery, MFV: Mean flow velocity, PINF: Personal and current information. * p < 0.05-- significant

Table 4: changes in MCA MFV before, during anesthesia and during on-pump period

	Difference	p value
Rt. MCA MFV before and during anesthesia	35.3 ± 17.2	< 0.001*
Rt. MCA MFV during anesthesia and on-pump period	-14.1 ± 19.6	< 0.001*
Rt. MCA MFV before anesthesia and during on-pump period	21.2 ± 26.7	< 0.001*
Lt. MCA MFV before and during anesthesia	33.1 ± 12.5	< 0.001*
Lt. MCA MFV during anesthesia and on-pump period	-24.7 ± 15.4	< 0.001*
Lt. MCA MFV before anesthesia and during on-pump period	8.4 ± 24.4	0. 070

Lt.: Left, Rt.: Right, MCA: Middle cerebral artery, MFV: Mean flow velocity. * p < 0.05--significant

Table 5: Relation between cognitive functions and the MCA mean flow velocity

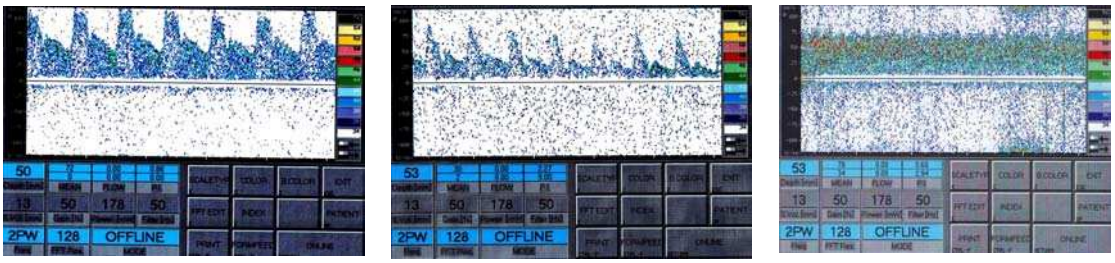
	RT. MCA MFV during anesthesia	LT. MCA MFV during anesthesia	RT. MCA MFV on-Pump	LT. MCA MFV on-Pump
Verbal IQ after 1 month	0.874	0.003*	0.674	0.978
Performance IQ after 1 month	0.264	0.031*	0.775	0.923
Total IQ after 1 month	0.837	0.004*	0.746	0.938
Personal and current information after 1 month	0.757	0.423	<0.001*	0.064
Orientation after 1 month	0.005*	0.185	0.061	0.446
Mental control after 1 month	0.694	<0.001*	0.196	0.471
Immediate recall after 1 month	0.657	<0.001*	0.701	0.396
Memory span for digits after 1 month	0.219	0.028*	0.372	0.057
Visual reproduction after 1 month	0.592	0.543	0.252	0.851
Paired associated learning after 1 month	0.005*	0.309	0.100	0.190
Total Wechsler memory IQ after 1 month	0.777	0.011*	0.885	0.679
Total HDRS after 1 month	0.075	0.058	0.098	0.465
Verbal IQ after 3 months	0.954	0.001*	0.516	0.693

Table (5) continue:

	RT. MCA MFV during anesthesia	LT. MCA MFV during anesthesia	RT. MCA MFV on-Pump	LT. MCA MFV on-Pump
Performance IQ after 3 months	0.600	0.010*	0.974	0.471
Total IQ after 3 months	0.870	0.001*	0.654	0.960
Personal and current information after 3 months	0.511	0.130	0.051	0.712
Orientation after 3 months	0.048*	0.670	0.415	0.048*
Mental control after 3 months	0.211	<0.001*	0.015*	0.007*
Immediate recall after 3 months	0.420	0.002*	0.411	0.942
Memory span for digits after 3 months	0.477	0.002*	0.669	0.289
Visual reproduction after 3 months	0.421	0.078	0.465	0.732
Paired associated learning after 3 months	0.677	0.005*	0.413	0.770
Total Wechsler memory IQ after 3 months	0.295	<0.001*	0.904	0.784
Total HDRS after 3 months	0.959	0.012*	0.209	0.052

HDRS: Hamilton Depression Rating Scale, IQ: Intelligent Quotient, Lt.: Left, Rt.: Right, MCA: Middle cerebral artery, MFV: Mean flow velocity. * p < 0.05-- significant

Figure 1: TCD for MCA before anesthesia, during anesthesia and during on-pump period



Discussion

No fewer than six pathophysiologic effects of cardiopulmonary bypass have been established in the world literature. These are (1) activation of the complement cascade with increased capillary permeability (Singh et al. 1980), (2) metabolic acidosis, (3) severe interstitial fluid accumulation, (4) elevated systemic vascular resistance, (5) arteriovenous shunting, and (6) impaired brain oxygenation (Runge et al. 1992). The National Institutes of Health has recognized that there are important problems with cardiopulmonary bypass and emphasizes the prevalence of neurologic damage produced by conventional cardiopulmonary bypass, particularly in patients who are extremely young or older than 60 years of age (Kirklin et al. 1983). Cognitive memory loss is now an acknowledged complication of the procedure, particularly in patients older than 60 years. There is no longer a question of whether this occurs, only questions of its frequency and what can be done about it (Runge et al. 1992).

Cognitive performances after cardiac operations may be influenced by several important factors. First, scores may be affected by the cardiac operation itself. Our results provide typical examples of this postoperative cognitive change. Second, the effects of practice may influence results, with group performances often improving when psychometric tests are administered repeatedly (Feinstein et al. 1994). Practice effects can be minimized by the use of alternative forms and long follow-up intervals or controlled by a comparison group that undergoes the same assessments at the same time points and this we applied in our study.

Most of the studies reporting late cognitive decline after CABG did not include a control group. It is therefore difficult to determine if the cognitive changes are caused by cardio-pulmonary bypass with general anesthesia years earlier or caused by normal aging, development of Alzheimer's disease or other causes. The choice of appropriate control for CABG has been controversial. The presence of diabetes, hypertension and other cardiovascular risk factors has increased in the candidates for CABG. Therefore ideal controls should also include patients with similar frequency of risk factors for cerebrovascular disease. Neither duration nor the severity of these risk factors can be easily quantified and how these risk factors translate into cerebro-vascular disease is also unknown (Vibha et al. 2006).

Our results showed that the patient group performed lower at baseline than did the healthy controls in the cognitive domains of immediate recall, memory control, memory digit span and paired associate learning. This type of cognitive profile is comparable to that seen in prospective studies of patients with MRI-defined subcortical cerebrovascular disease (Dixon and Raz 2000). Other large-scale epidemiologic studies of community-dwelling individuals indicate that the presence of risk factors of cardiovascular disease, such as hypertension and diabetes, is associated with decline in cognitive performance over time even in the absence of cardiac surgical intervention. Thus, our conclusion is that CABG patients, like similar patients, with long-standing coronary artery disease, have some degree of cognitive dysfunction secondary to cerberovascular disease before surgery (McKhann et al. 2005).

Another possibility is that the surgical group has a falsely baseline because of adverse testing conditions associated with the proximity to surgery, such as anxiety and depression. This possibility may explain the significant difference between the surgical group and healthy control on the total Hamilton Scale score for depression, which we found in our study. However, this would not explain why only specific cognitive domains, such as visual reproduction and memory control in contrast to other domains as performance IQ, are lower preoperatively (McKhann et al. 2005).

The change between baseline, one month and three months in the 2 groups is of some interest. In our study, there was a cognitive decline after one month postoperatively, this could be explained by the previous psychopathological factors of CABG stated before, especially that all of our patients underwent on-pump procedure. This was supported by most of the studies as that done by Van Dijk et al. (2002) who showed that there were significant differences in the incidence of decline between patients having conventional on-pump versus off-pump surgery at 3 months.

Cognitive dysfunction has been reported to persist for several months or even years after CABG (Taggart et al. 1999). In our study the cognitive performances of the patient group declined 1 month after the operation then improved 3 months postoperatively, nearly it returns to base line. Thus, we did not find selective effects of CABG on longitudinal cognitive performance. In general, these findings are in keeping with data from other studies by Vingerhoets et al. (1996) and Toner et al. (1998) that report significant improvements in cognitive function late after cardiac operations and the clinical impression that cognitive impairment is now uncommon late after cardiac operations.

The interpretation of these findings is that patients in the current study have known cardiovascular disease, and thus it is likely that at least some of these patients also have underlying cerberovascular disease, although we exclude neurological deficit by clinical examination. Those patients may have deficits that appear on imaging studies. This is supported by study of 421 patients scheduled for CABG, in which MRI was obtained preoperatively, 126 (30%) had small brain infarctions and 83 (20%) had multiple, larger infarctions. In addition, they found those with infarctions were more likely to have lower cognitive performance before surgery (Goto et al. (2001).

The discrepancy between decline in test performance and functional decline is also expressed by the methodological difficulties of defining a cognitive deficit. Mahanna and colleagues (1996) demonstrated the enormous influence of the definition of cognitive deficit that is chosen by applying five different definitions on the same patient sample. The single-case analysis technique, recommended in the consensus statements (Murkin et al. 1995, Murkin et al. 1997), uses the patient as his or her own control and defines a cognitive deficit as a 20% decrease in at least 20% of the tests. This method also has some drawbacks. In the first place, reducing the continuous test scores to a dichotomous outcome measure (presence of a 20% decrease or not) is a "costly" way of data handling that reduces statistical power and may have made several randomized studies fail to reach statistically significant results. The 20% decrease rule is as arbitrary as the 1

standard deviation decrease rule. The problem may be overcome by refraining from "dichotomizing" data and just calculating how much the patient's performance deviates from the expected (baseline or control group) performance (Van Dijk et al 2000). Our study design involves control group, so, we did not need to rely on arbitrary criteria for determining change of cognition. This is a strength that makes our study different.

We used TCD to measure blood flow velocity bilaterally in the middle cerebral arteries (MCAs) because it is the only continuous means of measuring changes in cerebral hemodynamics noninvasively and has become an essential part of neurologic monitoring (Edmonds et al. 1996). A close relationship between changes in cerebral blood flow and changes in blood flow velocity as measured by TCD has been demonstrated in patients with symptoms suggesting cerebrovascular disease and in patients during cardiac surgery (Van der Linden et al. 1991, Dahl et al. 1992, Trivedi et al 1997). In our study we found that the MCA mean flow velocity decreased significantly during anesthesia on both sides then it was increased again significantly during the on-pump time. Although the changes were on both sides, we found that the cognitive decline was related more to the decreased lt. MCA mean flow velocity during anesthesia.

There is no longer a question of whether cognitive decline after CABG occurs, but the actual cause of it may still be debatable (Vibha et al. 2006). The reason for this uncertainty about the cause comes from data from earlier studies that suggested that CBP was not the sole cause of cerebral dysfunction after cardiac operations (Smith 1988, Hammeke and Hastings 1988, Vingerhoets et al. 1997). Collectively, these studies question the established dogma that CPB is responsible for cognitive impairment after cardiac operations, at least in patients undergoing closed operations and with at least moderate ventricular function. If, however, CPB is not specifically responsible for cognitive impairment at early and late follow-up, what alternative intraoperative components common to both operations could be involved? Several candidates present themselves that include hypotension, general surgical injury, and anesthesia.

Although severe intraoperative hypotension may cause cognitive dysfunction, most prospective studies have failed to confirm this when mean arterial pressure is maintained above 50 mm Hg. (Ellis et al. 1980, Sotaniemi et al. 1981, Savageau et al. 1982, Arom et al., 1989 Slogoff et al. 1990), a level at which cerebral autoregulation normally occurs. In our study the mean blood pressure was maintained at 50 to 60 mm Hg.

The contribution of the general effects of surgical injury warrants consideration, given previous findings that patients undergoing major noncardiac operation also showed cognitive dysfunction (Smith 1988, Hammeke and Hastings 1988, Vingerhoets et al. 1997). These studies cannot, however, distinguish the effects of surgical injury from those of concomitant anesthesia.

General anesthesia per se can result in postoperative cognitive impairment in patients undergoing non-cardiac surgery. In a study on patient aged 40-60 year, 19% were found to have cognitive decline 7 days after surgery compared to only 4% in matched controls (Johnson et al. 2002). By 3 months after surgery, cognitive decline was minimal and not different from control.

In the largest trial to date that investigated the effects of general and epidural anesthesia in orthopedic patients, 5% of all patients showed clinically significant deterioration on a large battery of neuropsychologic tests at 6 months (Williams-Russo et al. 1995). Furthermore, 27% of all patients showed a clinically important deterioration in verbal memory at 6 months.

Although it is generally recognized that anesthesia can produce short-term cognitive dysfunction (Karhunen and John 1982, Herbert et al. 1987), the long-term effects remain open to question. Furthermore, when evaluating the effects of anesthesia, most studies typically consider only the effects of a single agent. Few, if any, consider the potential for the cumulative and/or interactive effects of different agents commonly used (Halsey 1995). As emphasized by Klafta and colleagues in 1995, the typical anesthetic regimen for cardiac operations produces "deeper anaesthesia than is normally required for non-cardiac operation." Taggart et al. (1999) speculate that this cognitive dysfunction might result from anesthetic dependent cerebral ischemia or disturbances of cerebral autoregulation.

This raises an important question about whether the cognitive impairment is due to the anesthetic drugs used or due to the decrease in cerebral perfusion as noticed in our study during anesthesia, or both. Taggart et al. (1999) suggest that the particular anesthetic regimen in association with nonspecific effects of the general operation may be responsible for producing the common pattern of cognitive dysfunction after cardiac operations. To resolve this issue would require submitting age-matched patients to the same anesthetic regimen but without operation, not an ethical proposition.

So, could CABG per se be innocent from the postulation that it is the cause of cognitive dysfunction? These questions need to be addressed in further studies to answer them.

Limitations

A potential weakness of our study was that the neuropsychologic tests were performed by one observer who was not blinded to the groups. In addition to the fact that many of the neuropsychologic tests are objective and quantifiable assessments of cognitive performance and not easily influenced by the examiner, our postulated a priori bias was that the control group would perform better than the patient group. Second, the TCD done was not directed for emboli detection which is an incriminated factor in cognitive affection. Nevertheless, it helped to alarm the anesthetist for the cerebral blood flow during anesthesia.

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Authors

El-Batrawy A.
Lecturer of Psychiatry
Ain Shams University**.**

Hazzou A.
Lecturer of Neurology
Ain Shams University**.**

Mostafa M.
Assistant Professor of Cardiothoracic surgery
Cairo University.

Reda W.
Assistant Professor of Anesthesia
Ain Shams University.

Tobacco Dependence in Psychiatric Disorder

Altaweel M.

Abstract:

Rates of dependence in psychotic population appears to be high, and it has been estimated that patients with mental illness consume 44.3% of all cigarettes in the United States. The present study aimed at studying how can psychiatric disorders (schizophrenia, bipolar disorder, and substance abuse) affect the dependence of nicotine. The study included 95 patients from the outpatient clinic in Kuwait psychological medicine hospital, (39 schizophrenic,36 bipolar disorder and30 substance abuse), in addition to similar number of healthy controls. Both patients and control were assessed for nicotine dependence using DSM IV criteria, as well as Fagerstrom test for nicotine dependence. 25 schizophrenic patients showed nicotine dependence, compared to 6 control subjects while 23 patients out of 30 bipolar compared to only 6 controls, and 24 substance abuse patients out of 30 showed positive nicotine dependence compared to only 8 controls. Higher rates of nicotine dependence are observed in various psychiatric disorder patients.

Introduction

Large population-based studies in the United States report the current rate of smoking to be approximately 22% to 28% (CDC, 2004; Grant et al., 2004). Smokers with current psychiatric disorders have significantly higher rates of smoking (41% on average), and it has been estimated that patients with mental illness consume 44.3% of all cigarettes in the United States (Lasser et al., 2000).

Data from the National Co morbidity Survey revealed that whereas the population prevalence of current smoking among those with no mental illness was 22.5%, some 41% of those reporting a mental illness were current smokers. People with mental illnesses also consumed more cigarettes -- current smokers without mental illnesses had a mean peak consumption of 22.6 cigarettes per day, compared with 26.2 by those with a mental illness. Furthermore, those with a diagnosable psychiatric disorder consume an estimated 34% to 44% of all cigarettes smoked in the United States.

Rates of dependence in psychotic populations also appear to be high (Dalack et al., 1998; Kalman et al., in press). Smokers with comorbid psychiatric or substance use disorders are less likely to attempt quitting (Lasser et al., 2000) and have higher risk of developing smoking-related illnesses (Hurt et al., 1996; Lichtermann et al., 2001).

There have been several hypotheses to explain the high rates of smoking among people with psychiatric and substance use disorders. One hypothesis is that genetic factors influence vulnerability to both smoking and these disorders (Kendler et al., 1993). Two, certain environmental factors (e.g., stress, poverty) are associated with increased smoking and the onset of symptoms of psychiatric disorders. Three, people with psychiatric or substance use disorders use smoking as a way to self-medicate clinical symptoms, side effects of psychiatric medication or cognitive deficits (Chambers et al., 2001; Sacco et al., 2004).

Nicotine stimulates the release of several neurotransmitter systems, including dopamine, norepinephrine, 5-hydroxytryptamine (5-HT), glutamate, γ-aminobutyric acid (GABA) and endogenous opioid peptides, and acts as an agonist on presynaptic nicotinic acetylcholine receptors (nAChRs), which are stimulated endogenously by acetylcholine (Picciotto, 2003). Although chronic exposure of agonists typically produces receptor downregulation, chronic nicotine administration causes a paradoxical upregulation of nAChRs through rapid desensitization followed by receptor inactivation (Gentry and Lukas, 2002). After a short period of abstinence (e.g., overnight), nAChRs are resensitized and once again responsive to nicotine. This may explain why many smokers tend to report the first cigarette of the morning as their most satisfying.

The dopamine reward system is associated with addiction to drugs of abuse, including nicotine (Volkow et al., 2002). Nicotine is thought to be reinforced by stimulating nAChRs in the ventral tegmental area of the midbrain that project to the nucleus accumbens, an important limbic area thought to be involved in drug reinforcement and reward. Further, these neurons project to the prefrontal cortex, which is thought to directly influence cognitive states, such as arousal and cognitive functioning.

***Background*:**

Although rates of cigarette smoking have been found to be higher in schizophrenic and depressed patients than in the general population, data regarding rates of bipolar patients are limited. This study further examines the relationship between bipolar disorder and smoking and compares the rate of smoking in bipolar disorder patients with rates in schizophrenic patients and in the general population

Aim of the Work

To study whether psychiatric disorders (Schizophrenia, Bipolar disorders, and substance abuse disorder) affects the dependence of nicotine or not, and how can different types inside a single disorder differs as regards the rate of abuse of nicotine

Methods

Assessment of 95 patients taken from the out patient clinic in the Kuwait psychiatric hospital , randomly chosen as every other one coming to the clinic in a period of 3 weeks. Complete psychiatric and substance use evaluations was done using DSM-IV semistructured interview. Substance abuse was excluded from the sample exception the substance abuse group, where any other axis I psychiatric disorder was excluded. Thirty nine patient was diagnosed with schizophrenia according to DSM-IV and only 34 agreed to continue the interview. Out of 36 patient diagnosed with bipolar disorder only 30 patient went on the rest of the interview, and all 30 substance abuse subject diagnosed with DSM-IV criteria continued the interview. Nicotine dependence was determined by daily smoking of 10 to 40 cigarettes according to DSM-IV resulting in tolerance to smoking effect and in the presence of withdrawal symptoms after cessation of smoking. Also, assessment of smoking behaviors did include self-report of cigarette and other tobacco use over the past 30 days and surrogate measures of smoking such as plasma nicotine levels (levels>15 ng/ml are considered dependence) (Benowitz et al., 2002).

Level of nicotine dependence was assessed through the Fagerstrom Test for Nicotine Dependence and the presence of nicotine withdrawal symptoms (e.g., irritability, cravings, headache, and fatigue) upon smoking abstinence.

Controls were chosen from patients family members matching nearly same age and sex, as family members has same socio-economic and educational status.

All control groups did undergo the general health questionnaire. (The Arabic version revised by okasha et al 1989, were the cut off point was changed and raised to 7 for the middle east.) to exclude any psychiatric disorder. Only those who did score under 7 was taken as controls. 70 control patients were interviewed as regard nicotine dependence using Fagerstrom test and as regard substance abuse using the DSM-IV criteria.

Results

Out of 34 patients with the diagnosis of schizophrenia, 25 showed nicotine dependence. The different types of schizophrenia were nearly equal with no significant difference among them as regard nicotine dependence. Out of 25 controls taken from schizophrenic families, only 6 showed nicotine dependence. (Table1).

Among 30 patient with the diagnosis of bipolar disorder, 23 showed positive nicotine dependence, and the number was more in the currently depressed subjects than those with the diagnosis of mania at the current interview. Only 5 out of the 23 normal controls taken from the bipolar patients families showed nicotine dependence. (Table2).

Twenty four out of the 30 patient with the diagnosis of substance abuse mostly poly substance use disorder (showed positive nicotine dependence). Out of 22 normal control subjects from families of substance abuse patients only 8 showed positive nicotine dependence (Table 3).

It was shown clearly in table 4 that patients with disorganized schizophrenia had the greatest number of dependence with 13 patients out of 25 patient nicotine dependent schizophrenics, followed by paranoid type schizophrenia with 9 patients and only 3 male patients with undifferentiated schizophrenia showing nicotine dependence. Male / female difference was very apparent in both disorganized and undifferentiated schizophrenics. Again table 2 made it clear for bipolar patients that the currently depressed 16 patient was the leading in nicotine dependence with a clear difference than those with a current manic episode 9 patients.

Table 5 showed the relation of symptomatology to nicotine dependence severity, and it was found that negative symptoms, and anxious mood to be the most leading association with nicotine dependence. As 9 patients out of 25 schizophrenics showed negative symptoms and 11 out of the 25 nicotine dependent schizophrenics had anxious mood according to DSM IV diagnostic criteria, and depression followed anxiety in its relation to nicotine dependence. However, Vulnerability to Extra pyramidal symptoms was highly related to nicotine dependence and to the severity of smoking as it showed that 17 out of 25 nicotine dependent schizophrenic are vulnerable to extrapyramidal symptoms in response to antipsychotic medication.

Table 1: number of positive nicotine dependent subjects among both schizophrenic and control groups.

		Control	Cases	Total
schiz-case	Non Smokers	19	9	28
	Smokers	6	25	31
Total		25	34	59
Pearson Chi-Square		Value	Exact Sig. (1-sided)	
		14.174(b)	.000	

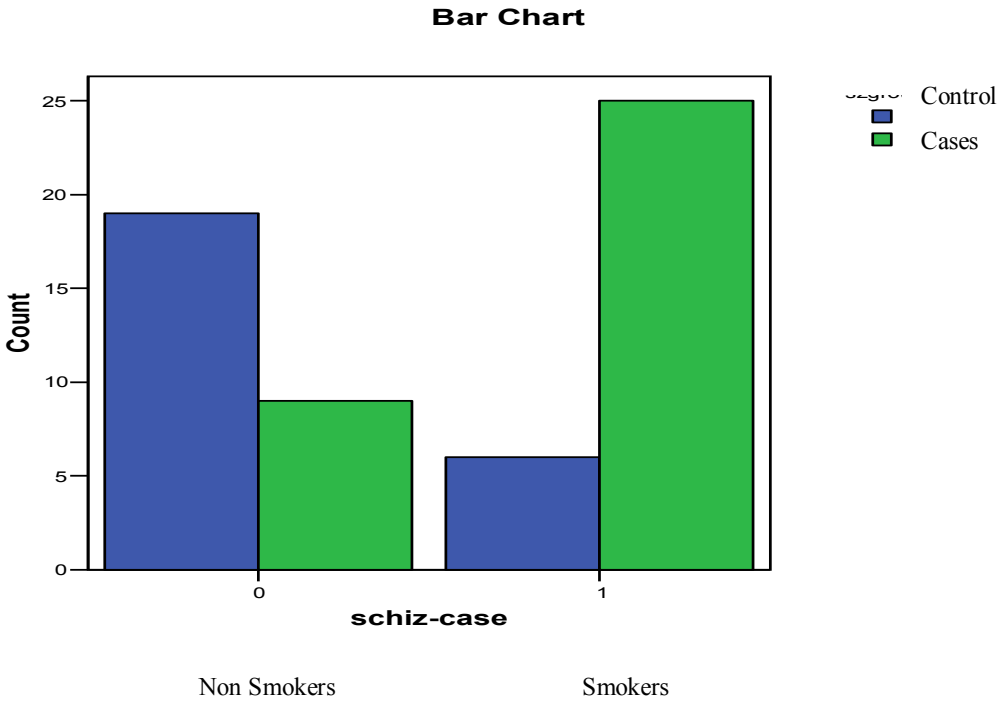

Table 2: number of positive nicotine dependent subjects among both bipolar and control groups.

		Control	Cases	Total
bip-case	Non Smokers	17	7	24
	Smokers	6	23	29
Total		23	30	53
Pearson Chi-Square		Value	Exact Sig. (1-sided)	
		13.442(b)	.000	

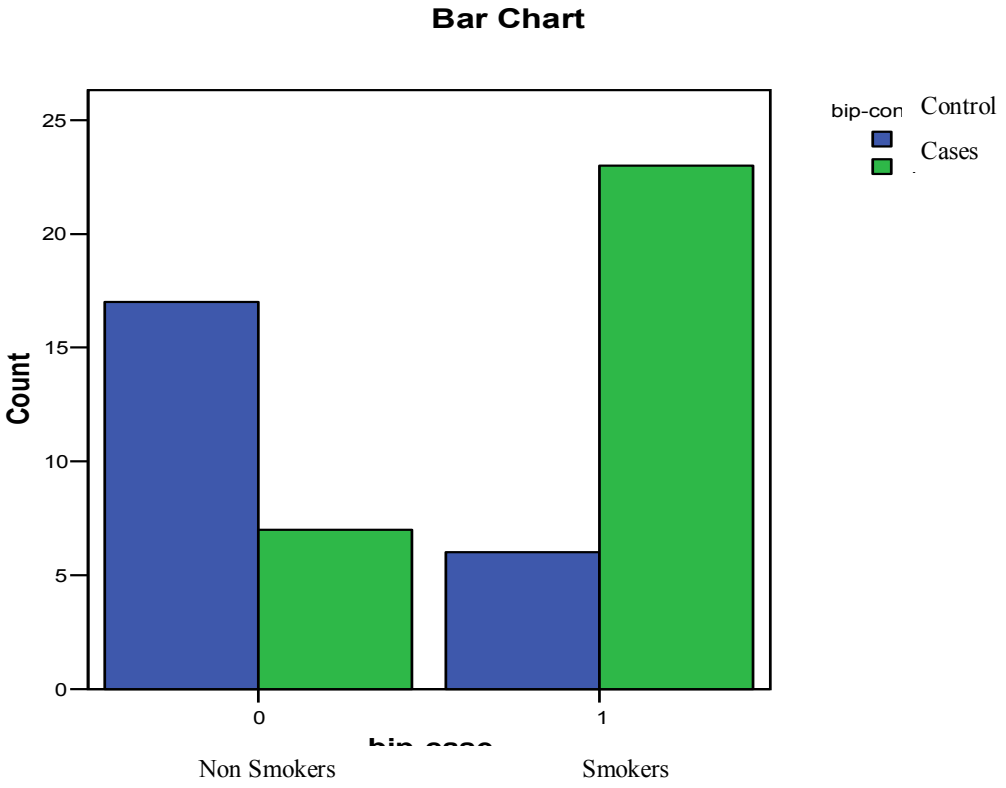

Table 3: number of positive nicotine dependent subjects among both Substance abuse and control groups.

		Control	Cases	Total
subst-case	Non Smokers	14	6	20
	Smokers	8	24	32
Total		22	30	52
Pearson Chi-Square		Value	Exact Sig. (1-sided)	
		10.211(b)	.002	

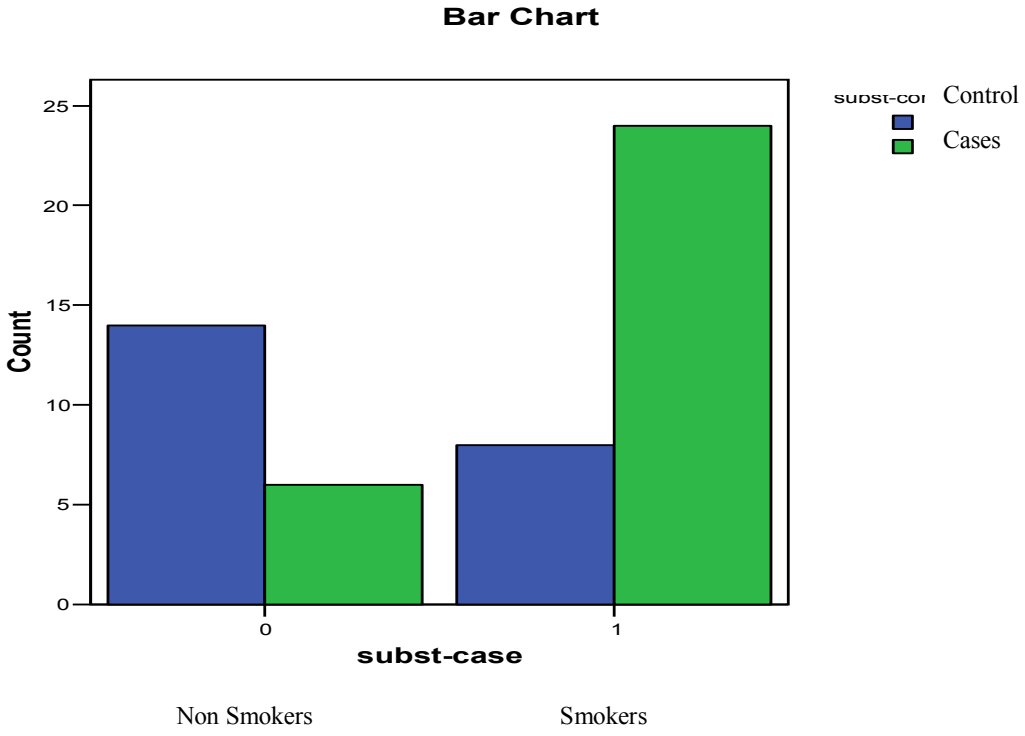

Table 4: Nicotine dependence in subtypes of schizophrenia and bipolar disorder.

	Schizophrenia						Total
Type	Disorganized		Undifferentiated		Paranoid		
Gender	Male	Female	Male	Female	Male	Female	
No.	*8/32%*	*5/20%*	3/12%	0/0%	4/16%	5/20%	25
Total	*13*		3		9		
	Bipolar disorder						
Type	Current Manic		Current Depression				
No.	*5/22%*	*3/10%*	11/48%		4/20%		23
Total	*9*		16				

Table 5 Description of variables in 25 patients with schizophrenia, according to their nicotine dependence status: non-smokers (NS), mildly dependent smokers (MDS) and highly dependent smokers (HDS)

Variable	25 patients	7 NS	10 MDS	8 HDS
Presence of symptoms				
Negative	9 (37%)	3	3	3
Positive	7 (30%)	2	2	3
Disorganised	3 (14%)	1	1	1
Excited	4 (20%)	1	1	2
Anxious	11 (47%)	3	4	4
Depressive	7 (31%)	3	2	2
Vulnerability to extrapyramidal symptoms	17 (69%)	5	5	7
Presence of akathisia	3 (14%)	1	1	1

NS = non smokers, MDS = mild smokers, HDS = Heady smokers, D.F = degree of freedom

Discussion

In our results(Table 1) , among 34 schizophrenic patients 25 showed positive nicotine dependence as opposed to control, who showed only 6 positives. This opposed difference between patients and controls did record its highest values in the bipolar population (Table 2) , whereas among 30 patient studied with bipolar disorder studied 23 showed positive nicotine dependence compared to only 6 among 21 controls showed positive dependence. Substance

abuse (Table 3) did not show great difference to schizophrenia where 19 out of 30 patients with substance abuse showed positive results opposed to 8 among controls.

This results was nearly comparable to the highest smoking prevelances found for people with bipolar (68.8%), psychotic (49.4%) and substance use disorders (49.0%) by Lasser et al., 2000.

Female in present study showed clear difference than male in dependence of nicotine, being less in number in both patients and controls and this goes with the cultural difference between male and female , and also showed the tight supervision and disapproval of smoking among females from families. Still there was clear difference between female patients and female controls.

Nicotine administration has been shown to improve neurocognitive deficits in schizophrenia (Sacco et al., 2005), attention-deficit/hyperactivity disorder (Conners et al., 1996; Levin et al., 1996) and Alzheimer's disease (Potter et al., 1999). And this can explain the high prevalence of nicotine dependence and suggests a potentially critical role for nAChR stimulation in mediating cognitive dysfunction in these specific disorders (Sacco et al., 2004). Interestingly these effects are not consistently observed in healthy smoking controls. A series of studies have shown that an auditory gating measure (P50) deficit associated with schizophrenia is mediated by nicotine and smoking (Leonard et al., 2002), and that these effects are related to activation of one form of nAChR (α7 nAChR [CHNRA7]) and that the expression of this receptor appears to be dysregulated (Leonard et al., 2002). Potential Explanations for the Association between Smoking and Schizophrenia

The causes of the very high prevalence of cigarette smoking in individuals with serious mental illnesses are complex and multifactorial. Most of the literature examining reasons for the association between smoking and schizophrenia focuses on the neurobiologic effects of nicotine, such as its interactions with dopaminergic circuits. Consuming nicotine may ameliorate some of the negative symptoms of schizophrenia, such as amotivation, anhedonia, and social isolation and this could explain our finding recorded in (Table 5) that showed that 9 out of 25 nicotine dependant schizophrenic subjects did show negative symptoms and it came as the second cluster of symptoms to increase nicotine dependence among our patient sample. Nicotine also may improve auditory gating impairments in persons with schizophrenia, which in turn may enhance attention, sensory processing, and the ability to interact with their environments. Again psychological factors may influence use of nicotine among patients

When we studied the rate of nicotine dependence among the subtypes of schizophrenia (disorganized, and paranoid) and bipolar disorder (either manic or depressive episodes) in table 4. Disorganised schizophrenia showed the highest rates of dependence among the schizophrenic population with 13 patients out of 25 and this in a part can be explained by the increased cognitive deficit symptomatology and flattening of affect among disorganized compared to other types. While the currently depressed patients showed a higher rate of dependence than those with current mania. As there was 16 currently depressed bipolar patients

(70%) compared to 7 patients with current manic episode. A relationship between nicotine dependence and depression has been seen in both epidemiological and clinical samples done by Brown et al 1993. Going also with our results as shown in table 4, Huges et al 1996 found that a clinical sample of depressed outpatients where twice as likely to smoke as the general population. Again individuals in a study by Covey et al 1993 with a lifetime history of depression were more likely to have smoked in their life time (76%) versus 52% in non depressed, the finding was more significant among male smokers. also in(Table 5) it was clear that depression was the third cluster of symptoms that caused cigarette smoking among schizophrenia, the thing that goes with Glassman A H- 1993 who noticed that persistant depressive symptoms in schizophrenia may influence the prevalence of smoking.

Although some research has reported that smoking cessation can lead to a reemergence of depressive symptoms (Covey et al., 1997; Glassman et al., 1993), other studies have questioned this relationship (Thorsteinsson et al., 2001). However, a past history of major depression does not appear to influence tobacco treatment outcomes (Hayford et al., 1999).

It is undoubtedly expected for substance abuse disorder population to show high prevalence of nicotine dependence, and to show an equal rate among males and females, in our study, female substance use patients were quite few, and there was no explanation why female patients seek less psychiatric help.

The development of effective strategies for promoting smoking cessation in schizophrenia is of great importance given the high rates of smoking and cessation failure in this patient group. The nicotine transdermal patch (NTP) is associated with smoking cessation rates of 27% to 42% in smokers with schizophrenia (Chou et al., 2004). Further, use of the nicotine nasal spray, which produces higher plasma levels of nicotine, is associated with reduction of withdrawal and craving, and smoking cessation in smokers with schizophrenia (Williams et al., 2004) and it may help in recovery of cognitive dysfunction, hence putting hope in recovery of schizophrenia.

Although cigarette smoking may partially ameliorate specific psychiatric symptoms (such as negative symptoms) and cognitive measures,[the general "self-medication" hypothesis (improvement in negative, cognitive, or depressive symptoms and reduction of antipsychotic side effects) has not been supported by all studies.(Dalak et al 1998) The higher prevalence of smoking found among individuals (before the onset of their illness) who later develop schizophrenia may further indicate that impaired nicotinic neurotransmission is involved in the pathophysiology of schizophrenia.

We suggest that an association exists between smoking and psychotic symptomatology, and not with the categorical diagnosis of either schizophrenia or bipolar affective disorder.

Appendix

Fagerstrom test for Nicotine dependence

1. Are you evaluating a person who smokes cigarettes for how severe a nicotine dependence the person has? (Y or N)
2. number of minutes after the person wakes up before s/he smoke the first cigarette

3. number of cigarettes smoked by the person daily
4. Is it difficult for the person to refrain from smoking in places where smoking is forbidden? (Y or N)
5. Is the first cigarette of the day the one cigarette that the person would most hate to give up? (Y or N)
6. Does the person smoke more frequently during the first hours after waking than during the rest of the day? (Y or N)
7. Does the person smoke even when so ill that s/he must stay in bed most of the day? (Y or N)

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Authors:

Altaweel M.
Lecturer of Psychiatry
Faculty of Medicine
Cairo University

Address of Correspondence:

Altaweel M.
Lecturer of Psychiatry
Faculty of Medicine
Cairo University

Cognitive profile of patients with newly diagnosed Parkinson's disease

Abo-El-Naga Y

Abstract

Cognitive deficits can occur even in the early stages of Parkinson disease (PD). In many instances these deficits may not be clinically apparent, but they are detectable with specific neuropsychological tests. However, the exact pattern of these impairments and their frequencies are still subjects of considerable controversy. To investigate the cognitive profile of patients with newly diagnosed Parkinson disease (PD) and to determine the demographic and medical variables those contribute to the cognitive outcome. Forty three consecutive patients with newly diagnosed PD and 30 healthy controls were given a neuropsychological test battery investigating psychomotor speed, attention, language, memory, executive and visuospatial functions. Patients also received quantitative ratings of motor symptom severity. Neuropsychological performance of PD patients was compared with that of healthy controls and with available normative data. Independent demographic and clinical predictors of cognitive impairment were identified with multiple logistic regression analysis. Relative to controls, PD patients performed significantly worse on most cognitive measures. However, further analysis revealed that group differences in cognitive performance could mainly be explained by measures of immediate memory and executive function. Comparison with normative data showed that impairments were most frequent on measures of executive function, memory and psychomotor speed. In all, 25.6% of PD patients (6.7%of controls) displayed defective performance on at least three neuropsychological tests and were classified as cognitively impaired. Late onset of disease was an independent predictor of cognitive dysfunction in PD.The observed cognitive impairments in patients with newly diagnosed Parkinson disease are more than expected for normal aging, with deficits being most prominent in the domains of memory and executive functions. Older age at disease onset is likely to be an important determinant of cognitive dysfunction in Parkinson disease.

Introduction

Parkinson's disease (PD) is an age-related, progressive neurodegenerative disorder initially characterized by resting tremor, rigidity, or bradykinesia *(Gelb et al, 1999)*. Cognitive changes can complicate the long-term management of PD and are estimated to occur in 20% to 40% of all diagnosed patients who have PD, leading to a diagnosis of Parkinson's disease with dementia (PDD). Alternatively, cognitive deficits can occur even in the early stages of Parkinson disease (PD) *(Elmer, 2004)*. In many instances these deficits may not be clinically apparent, but they are detectable with specific neuropsychological tests. Some deficits resemble those seen in patients with frontal lobe damage, which is consistent with the anatomic model of basal ganglia thalamocortical circuits *(Louis, 1997)*. However, the exact pattern of these impairments and their frequencies are still subjects of considerable controversy. In support of the hypothesis of "frontal-type dysfunction," isolated deficits have been found in newly diagnosed, nonmedicated PD patients on tests known to be sensitive

to frontal lobe damage *(Mayeux et al, 1981; Dooneief et al, 1992; Cummings et al, 1988 and Fenelon et al, 2006)*. Other studies, however, have found a more generalized pattern of cognitive dysfunction *(Tandberg et al, 1996 and Aarsland et al 1999)*. Furthermore, some investigators found no evidence of "frontal deficit" in their sample, suggesting that such impairment is not a universal cognitive feature of early PD (*Tandberg et al, 1996)*. More over Regardless of the specific classification of cognitive impairment accompanying the extrapyramidal features of PD, dementia has a great impact on the course and management of PD symptomatology *(Elmer, 2004)*. In an attempt to resolve these discrepancies, we examined the frequency and pattern of cognitive impairments in a group of patients with newly diagnosed PD using a comprehensive battery of neuropsychological tests. In addition to comparing the patients' performance to that of healthy controls, standard scores were derived for each measure from published normative data to assess the cognitive profile in a more clinically meaningful manner and with greater external validity. Furthermore, we sought to identify demographic and clinical correlates of cognitive dysfunction in early PD.

Subjects and Methods

Subjects

The patient sample consisted of forty three patients with Parkinson disease (PD) who fulfilled the clinical criteria for the diagnosis of PD *(Calne et al, 1992 and Elmer, 2004)*. They were recruited from the neurology outpatient clinics of Saudi German hospital, Madinah Elmonawarah, King Saudi Arabia. Exclusion criteria were age of 85 years or older, global cognitive decline (Mini-Mental State Examination [MMSE] < 24), and the presence of somatic illness with a life expectancy of less than 1 year. Neurologic examination was conducted for all patients. At the time of the examination, 14 patients were not receiving any medication. Of the remaining 29 patients, 15 were treated with levodopa plus a peripheral levodopa-decarboxylase inhibitor, 6 with a dopamine agonist (pramipexol), two with levodopa in combination with a dopamine agonist (pramipexol in both cases), four with amantadine, one with levodopa in combination with a dopamine agonist and amantadine, and one with amantadine plus an anticholinergic drug. To calculate levodopa dose, we pooled different drugs in a levodopa equivalent dose (LED) *(Emre, 2003)*. None of the patients received antidepressants, benzodiazepines, or antipsychotics. None of the patients had undergone neurosurgical operation for relief of motor symptoms.

Thirty normal control subjects (NCs), who were neurologically intact and age matched to the PD patients, were also recruited. None of the controls had impairment in hearing and visual acuity, history of a major psychiatric disorder, head injury with loss of consciousness in excess of 1 hour, cerebrovascular disease or other CNS illness, drug or alcohol abuse, and were currently taking psychoactive medication. Control subjects underwent only neuropsychological assessment. Written informed consent was obtained from all subjects after the nature of the study was fully explained.

Procedure

Neuropsychological assessment was conducted within 1 to 4 weeks after the neurologic examination.

Neurological examination

A detailed neurologic examination was performed in all patients to check the diagnosis of PD. Information about the onset and course of the disease, initial symptoms, side of onset of disease, medical history, medication, and response to levodopa therapy was obtained with a semistructured interview. The severity of extrapyramidal symptoms was rated using the motor section of the Unified Parkinson Disease Rating Scale (UPDRS) *(Aarsland et al, 2005)*. The stage of disease was determined with the Hoehn and Yahr rating scale. The duration of disease was defined as the time between the appearance of the first symptom of PD as reported by the patient and the moment of assessment.

Neuropsychological assessment

Neuropsychological tests were administered in a fixed order during a period of 2 to 3 hours with suitable rest periods. In addition to assessment of global cognitive functioning (MMSE) *(Louis et al 1997 and Aarsland et al, 2000)* neuropsychological testing examined functions in six cognitive domains: psychomotor speed, attention, language, memory, executive functions, and visuospatial/constructive skills *(Rippon and Marder, 2005)*. Psychomotor speed was evaluated using the Wechsler Adult Intelligence Scale–Revised (WAIS–R), Digit Symbol test (This subtest of the WAIS-III presents the patient with a row of numbers one through nine, each paired with nonsense symbols (e.g., inverted T). Below this key are empty boxes with numbers above each box. The patient is required to transcribe the symbol corresponding to the number above the box as quickly as possible. This measure requires focused attention and switching behavior between the key and the target boxes. One advantage of this test is the extensive WAIS-III norms available on performance expectations) *(Levy et al, 2000)* and Trail Making Test Part A (This test requires the patient to connect randomly positioned numbered circles in numeric order as quickly as possible) *(Berg et al, 1982 and McKeith et al, 2005)*. Attention was assessed with an adapted version of WAIS–R forward and backward digit span (three trials were administered per length of digit strings; the score was the total number of correct responses for each condition, maximum 21) *(Berg et al, 1992)*, and Trail Making Test Part B (The patient is required to connect the circles in numeric and alphabetic order as quickly as possible, alternating between numbers and letters. Both Trail Making forms A and B require focused attention for successful performance) (*McKeith et al, 2005)*. Language function was examined with the Boston Naming Test (Patients are required to name 60 objects depicted in line drawings. The objects range from simple and common objects such as a tree to complex and uncommon objects such as an abacus. If a patient is unable to name an object, he or she is given a phonemic cue and a semantic cue) (BNT; short form, the score was extrapolated to the full-length score) *(Rubin e al, 1998)*. Memory was assessed with the Rey Auditory Verbal Learning Test (This test of verbal memory presents the patient with multiple trials of learning a list of 10 words. Following each presentation of the study list, the patient is asked to recall as many words as possible. Following the fifth repetition of this study list, a new study list is introduced followed by a recall trial. Following this recall, the patient is asked to recall as many of the words from the first list as possible. Finally, a recognition test is given if delayed recall is defective) (RAVLT; trials 1 to 5, 20-

minute delayed free recall and recognition of a list of 15 unrelated words) *(Biggins et al, 1992)*, Logical Memory Test (immediate and 20-minute delayed recall of two stories) *(Aarsland et al, 2001)*, the Wechsler Memory Scale III (WMS–III; faces recognition test immediate and 30-minute delayed recognition) *(Morris, 1993)*, and Visual Association Test (VAT; subjects are shown six pictures of two common objects; recall is tested without a delay by showing one object and asking what other object is missing; one point was awarded for each correctly recalled object; two trials are given resulting in a score range of 0 to 12) *(Morris et al, 2001)*. Executive functions were examined with the Modified Wisconsin Card Sorting Test (MWCST: Patients are presented with four "target" cards with simple colored designs that can be sorted by three concepts. The patients match probe cards with identical colored design to the target cards according to whatever concept they generate. The only feedback to the patient after each trial is whether his or her response is correct. The order of sorting concept is fixed, but unbeknownst to the patient, changes after a set number of correct responses. Thus, patients must be able to switch the concept they were using for the previous trials) *(Petersen et al, 1985)*, and WAIS–III Similarities (This subtest of the WAIS-III requires the patient to identify the common elements between seemingly uncommon stimuli. The test begins with simple problems (e.g., "How are an orange and banana alike?"), and progress to more difficult problems. Scoring awards full credit for complete abstractions, partial credit for concrete responses, and no credit for incorrect responses) *(McKhann et al, 1984)*. Visuospatial and constructive abilities were assessed with the Groningen Intelligence Test (GIT) spatial test (it is a test in which subjects were instructed to select the figures which they thought were needed to fill up a geometric design; one point was awarded for each correct response, range 0 to 20) *(Rockwood et al, 2000)*, and Clock Drawing Test (This test of visual construction in which the patient is required to draw a clock with all the numbers and "set" the clock at 20 minutes to four o'clock) *(National Institute on Aging, Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease, 1997)*.

Statistics

Differences in demographic and clinical characteristics between the PD and control groups were analyzed with independent two-tailed t-tests. Mann-Whitney test was used to analyze ordinal data, whereas the χ^2 test was used to analyze nominal variables. Cognitive dysfunction was considered to be present if performance on three or more neuropsychological tests was impaired. This criterion was chosen to minimize the possibility that compromised performance reflects a chance finding due to the large number of measures employed. Based on this criterion, PD patients were assigned into cognitively impaired or cognitively intact group.

Results

Demographic and clinical characteristics

PD patients were older and had lower educational level than controls (table 1). There were no differences between the groups with respect to sex distribution, MMSE score, or handedness. The average degree of motor disorder for the PD group fell within the mild-to-moderate range as

evaluated by the Hoehn and Yahr rating scale and the UPDRS motor section.

Neuropsychological performance of PD patients and control subjects

Patients with PD performed worse than controls on most of the neuropsychological measures employed in the present study (table 2). Within the domain of psychomotor speed, differences were significant for each of the two measures after univariate analyses. On tests of attention, univariate differences on Digit span backward and Trail Making Test B accounted for multivariate results. The PD group showed poorer performance on a measure of language function. Within the memory domain, PD patients performed consistently worse than controls on all tests except on measures of delayed word recognition and visual associative learning. Univariate differences with respect to MWCST number of categories, and WAIS Similarities test accounted for the multivariate differences in executive functioning. Multivariate difference between the PD and control groups in the visuospatial domain was due to GIT spatial task.

To determine which tests had greatest ability to differentiate PD patients from controls, we conducted a logistic regression analysis (forward stepwise method). All cognitive measures were entered into the regression analysis as independent variables, whereas the diagnosis (PD vs control group) was the dependent variable. This analysis identified four tests as best discriminating cognitive measures between the PD and control groups: WAIS Digit Symbol Test, RAVLT Trials 1 to 5, WMS–III Faces Immediate Recognition Test and Trail Making Test A. The Digit Symbol Test and Trail Making Test A involve a strong motor component and time constraints. Therefore, differences between PD patients and controls on these tests might be due to the motor disorder. To address this possibility, the logistic regression analysis was repeated excluding the Digit Symbol Test and Trail Making Test A. The results indicated that RAVLT Trials 1 to 5 and WMS-III Faces Immediate Recognition Test were measures that most effectively differentiated patients from controls. This set of variables correctly classified 77% of the cases (86% of PD patients and 63% of controls).

Clinical significance of cognitive impairments in PD patients

To determine to what degree cognitive impairments in PD patients were clinically significant, their performance on each measure was compared with published normative data. The highest frequency of impairment was observed on the Trail Making Test B (16%), followed by WAIS Similarities (14%), Digit Symbol Test (12%) and Clock Drawing Test (11%). The frequency of impairment was less than 10% on the remaining tests (table 3).

Frequency of cognitive dysfunction

Eleven (25.6%) PD patients exhibited cognitive dysfunction, defined as impaired performance on at least three neuropsychological tests (table 4). In comparison, two (6.7%) controls had evidence of cognitive impairment based on this criterion ($\chi^2 = 10.8$; $p = 0.001$).

The cognitively impaired PD group displayed deficits on measures of psychomotor speed, language, attention and executive functions, memory, and visuospatial abilities (figure 1). The lowest frequency of impairment was observed in the domain of language (22%), whereas deficits were found to be most frequent in

the domain of attention/executive functions (100%).

Demographic and clinical variables associated with cognitive dysfunction in PD

The cognitively impaired PD patients were older, disproportionally more male, had a later onset of disease, greater overall severity of disease and more severe axial symptoms and speech impediments than the cognitively intact PD group. There were no differences between the groups with respect to education, duration of PD, severity of tremor, bradykinesia, rigidity and facial mobility or functional status. No difference was observed between cognitively intact and cognitively impaired PD groups with regard to the MMSE score, suggesting mild degree of cognitive dysfunction (table 5).

Those variables shown to be associated with cognitive dysfunction after univariate analyses were submitted to a multiple logistic regression model (backward stepwise method). Because all normative data sets used in this study include adjustment for effects of age, and thus age was accounted for already by the assignment of patients into cognitively intact and impaired groups, this variable was not included in the regression analysis. Furthermore, the UPDRS motor section score and the Hoehn and Yahr scale were not included in the analysis. Although these two variables differed significantly between cognitively intact and cognitively impaired patients in the univariate analyses, differences on these measures were probably due to axial impairment and speech disorder, because other motor symptoms were comparable across the two PD groups. Thus, four variables were submitted to the regression analysis: sex, age at disease onset, axial symptoms and speech disorder. The results showed that only age at disease onset was an independent predictor of cognitive dysfunction in PD (OR = 1.06; 95% CI = 1.01 to 1.12; $p = 0.02$).

Table (1) Demographic and clinical characteristics of Parkinson disease patients and healthy controls

Variable	Patients with PD	Healthy controls	p Value
n	43	30	
Sex, M/F	23/20	16/14	0.98
Duration of PD, mo	15.8 (9.7)		
Age	65.2 (10.1)	62.7 (7.3)	0.05
Education, y	11.7 (2.4)	12.4 (2.2)	0.04
Handedness, R/L	38/5	27/3	0.81
Mini-Mental State Examination	27.8 (1.6)	28.2 (1.4)	0.09
UPDRS (motor section)	16.7 (7.8)		
Hoehn and Yahr scale	1.8 (0.7)		

Data are means (SD) unless noted.
PD=Parkinson disease; UPDRS=Unified Parkinson's Disease Rating Scale.

Table (2): Neuropsychological test findings (raw scores) of PD patients and controls

Measures	PD (n = 43)		HCS (n = 30)		F	p-value	Cohen's d
	M	SD	M	SD			
Psychomotor speed – MANCOVA: F = 15.76; p < 0.001							
Digit Symbol test	36.9	12.0	49.8	10.9	61.41	< 0.001	-0.93†
Trail Making Test A	49.4	19.4	39.8	13.9	8.26	0.005	-0.55
Attention – MANCOVA: F = 4.58; p = 0.002							
Digit span forward	11.9	2.8	11.9	3.1	0.42	0.517	0
Digit span backward	7.9	2.6	9.5	2.7	11.99	0.001	-0.61
Trail Making Test B	136.5	84.4	86.9	31.2	8.79	0.003	-0.51†
Language							
Boston Naming Test	53.5	4.1	55.5	3.1	9.00	0.003	0.003
Memory – MANCOVA: F = 11.17; p < 0.001							
RAVLT trial 1-5	39.0	9.7	48.5	8.9	41.09	< 0.001	-1.01
RAVLT delayed recall	7.9	2.8	10.3	3.0	23.77	< 0.001	-0.83
WMS-III Faces immediate	31.4	4.3	34.7	3.8	23.49	< 0.001	-0.70
Visual Association Test	11.6	0.8	11.8	0.5	2.23	0.137	-0.29
Executive functions – MANCOVA: F = 5.19; p < 0.001							
MWCST, no categories	3.9	1.8	3.9	1.8	17.22	< 0.001	< 0.001
MWCST, no errors	10.2	5.7	7.7	5.7	4.25	0.041	-0.44
MWCST, no perseverations	6.2	6.1	3.4	4.3	7.02	0.009	-0.51
WAIS-III Similarities	20.6	6.0	24.5	5.0	19.93	19.93	19.93
Visuospatial/constructive skills – MANCOVA: F = 4.93; p = 0.003							
GIT spatial task	9.2	3.3	11.3	3.4	11.96	0.001	0.001
Clock Drawing Test	12.6	1.3	12.6	1.3	2.77	0.098	-0.33

MANCOVA=multivariate analysis of variance with age, premorbid IQ as covariates. †Cohen's *d* corrected for processing speed. RAVLT=Rey Auditory Verbal Learning Test; WMS=Wechsler Memory Scale; MWCST= Modified Wisconsin Card Sorting Test; WAIS=Wechsler Adult Intelligence Scale; GIT= Groningen Intelligence Test.

Table 3): Neuropsychological tests and percentages of impaired PD patients and healthy controls (HC) on each test. Impairment was defined as a score below –2SD of age and (if possible education) norms.

Measure	N*	% PD patients impaired	N	% HC impaired
Psychomotor speed				
Digit symbol test	106	12	70	1
Trail Making Test A	115	7	70	1
Attention				
Trail Making Test B	115	16	70	0
Language				
Boston Naming Test	114	9	70	6
Memory				
RAVLT trial 1 -5	115	1	70	0
RAVLT delayed recall	115	1	70	0
WMS -III Faces immediate	115	1	70	0
WMS -III Faces delayed	115	0	70	0
Visual Association Test	113	0	70	0
Executive functions				
MWCST, no categories	115	5	70	0
MWCST, no errors	112	0	70	0
MWCST, no perseverations	112	0	70	0
WAIS -III Similarities	115	14	70	4
Visuospatial/constructive skills				
GIT spatial task	115	9	70	4
Clock Drawing Test	115	11	70	4

RAVLT=Rey Auditory Verbal Learning Test; WMS=Wechsler Memory Scale; MWCST= Modified Wisconsin Card Sorting Test; WAIS=Wechsler Adult Intelligence Scale; GIT= Groningen Intelligence Test. *Varies due to missing values or unavailable norms for older subjects.

Table 4. Number of impaired tests and percentages of Parkinson disease patients and healthy controls demonstrating impairments

No. of tests impaired	Patients with Parkinson disease,%	Healthy controls,%
0	37.4	68.6
1	24.3	20.0
2	14.8	7.1
3	8.7	2.9
4	3.5	1.4
<5	11.3	

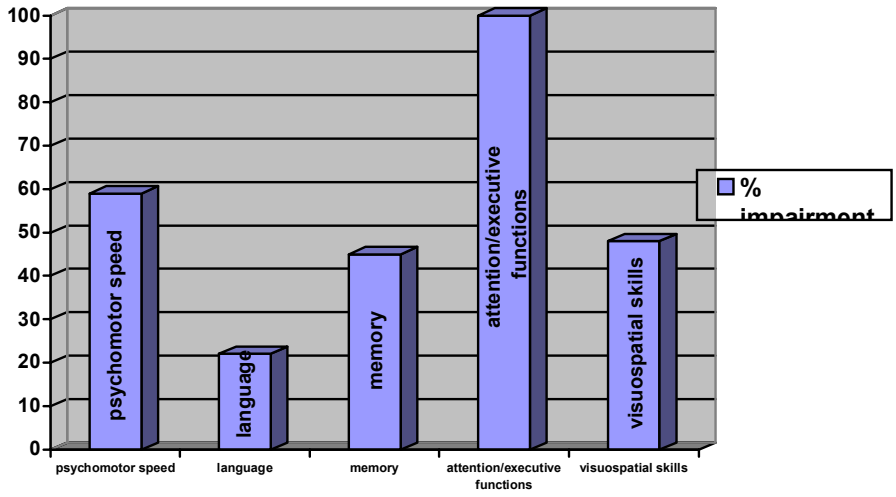

Figure (1): The frequency of impairment across different cognitive domains within the group of cognitively impaired Parkinson disease patients (n = 11).

Table (5): Demographic and clinical characteristics of cognitively intact and cognitively impaired PD patients.

Variable	Intact PD group (n = 32)		Impaired PD group (n = 11)		p-value
	M	SD	M	SD	
Age	62.9	10.4	68.3	8.1	0.02
Gender (M/F)	15/17		8/4		0.04
Education (years)	11.6	2.3	11.7	2.7	0.83
MMSE	28.0	1.5	27.4	1.6	0.06
Age at onset of PD	61.4	10.4	66.6	8.1	0.02
Duration of PD (months)	16.5	10.9	19.9	10.4	0.54
UPDRS (Motor section)	16.0	7.8	19.5	7.5	0.02
Tremor	2.4	1.9	2.2	1.9	0.56
Bradykinesia	5.9	3.1	7.1	3.3	0.08
Rigidity	2.9	2.2	3.7	2.3	0.08
Axial symptoms	1.5	2.0	2.4	1.9	0.01
Speech	0.4	0.5	0.7	0.7	0.03
Face	1.0	0.7	1.3	0.7	0.10
Hoehn & Yahr scale	1.7	0.7	2.1	0.7	0.01
LED (mg/day)[10]	132.9	144.8	186.7	128.8	0.09

UPDRS=Unified Parkinson Disease Rating Scale; MMSE=Mini Mental State Examination; LED=Levodopa equivalent dose.

Discussion

Most of the Available knowledge of cognitive dysfunction in Parkinson's disease (PD) has largely been obtained from studies of chronically treated patients in whom effects of disease chronicity, treatment, depression and dementia are confounding factors (*Cooper et al, 1991)*.

The present study examined the frequency and nature of cognitive impairments in a group of patients with newly diagnosed PD by comparing their performance on a comprehensive battery of neuropsychological tests with that of healthy control subjects. The results indicate that 25.6% of patients in our PD sample showed evidence of cognitive dysfunction. In comparison, 6.7% of control subjects were cognitively impaired. PD patients exhibited impaired performance on a wide range of standardized neuropsychological tests. However, further analysis of individual test performances revealed that deficits in the domains of memory, and attention and executive function constitute the core impairment. The proportion of PD patients with cognitive dysfunction in this study is somewhat lower than in one previous report, in which evidence of cognitive impairment was found in 36% of 159 newly diagnosed patients from a community sample *(Foltynie et al, 2004)*. However, we used more stringent criteria to define cognitive dysfunction; this is probably the reason for a lower frequency of impairment.

When the magnitude of cognitive deficits as expressed in effect sizes was taken into consideration, only deficits in certain aspects of memory function (i.e., immediate and delayed recall) and more complex tests of attention (i.e., Digit Symbol test) appeared to be substantial, whereas decrements on simple measures of attention and processing speed, as well as on tests of language and visuospatial functions were found to be minimal or moderate. Similar findings were observed when the logistic regression analysis was performed on the neuropsychological test battery. This analysis indicated that the Digit Symbol Test differentiated patients with PD from control subjects more effectively than other neuropsychological tests. After excluding tests that depend on processing speed, measures of immediate memory and executive functioning could account for many of the observed group differences in cognitive performance. In contrast, none of the tests purported to measure language and visuospatial functions were entered in the final regression model, suggesting that decreased performance of PD patients on these tests may not reflect truly independent deficits.

The highest frequency of clinically significant cognitive impairments in the PD group was observed on tests of attention and executive functions, and memory (see table 3). Thus, comparison to normative data confirms that deficits in attention and executive function and memory are most prominent features of cognitive dysfunction in patients with PD relative to other cognitive domains.

Although fairly frequent impairment was also observed on the Clock Drawing Test (11%), this finding should be viewed with some caution. The possible explanation for a relatively high rate of impairment on the Clock Drawing Test is that, in addition to measuring constructive ability, this test also involves aspects of executive functions.

Similarly, other measures used to assess visuospatial functions (i.e., GIT spatial task) also require one or more executive components such as spatial reasoning and strategy formation, which are likely to influence performance on these tasks. Thus, it is possible that the observed changes on visuospatial tasks may be due to executive deficits. Our findings from the logistic regression analysis also argue against an independent deficit in visuospatial abilities.

Our results indicate that later onset of disease is an independent predictor of cognitive impairment in patients with PD. This finding is in accordance with a number of cross-sectional *(Katzen et al, 1998)* and longitudinal studies *(Locascio et al, 2003)* in which older age at disease onset was reported to be associated with greater cognitive decline in patients with PD, although such a relationship was not consistently observed *(Huber et al, 1991)*.

In this study, levodopa equivalent dose (LED) was comparable across the cognitively impaired and cognitively intact PD groups. Moreover, only one patient in our sample was taking anticholinergic medication. Thus, cognitive disturbances in our PD patients cannot be attributed to drug treatment, but are likely to be directly related to the pathology of the disease.

Examination of the relationship between impairment of motor functions and the degree of cognitive disturbance in PD has been regarded as a standard clinical approach to determine whether the pathology underlying both types of disorders involves the same neural systems. In this study, the degree of cognitive dysfunction was not associated with the severity of any of the cardinal motor symptom triad of bradykinesia, tremor, or rigidity, which are thought to result from nigrostriatal dopaminergic deficiency. This finding suggests that cognitive dysfunction in early PD patients may reflect neuropathological changes that are distinct from those responsible for the motor disorder.

Similarly the findings of Cooper *et al, 1991* indicate that there is a dissociation of cognition and motor control in early PD and accordingly they suggest that cognitive dysfunction is largely independent of frontostriatal dopamine deficiency underlying motor disability. They concluded that the pathogenesis of the cognitive deficits shown here appears to involve extranstriatal dopamine systems or non-dopaminergic pathology.

Furthermore in the present study as additional support for this assumption is the lack of association between cognitive impairment and dopaminergic medication. In addition, the observation that cognitively impaired PD patients exhibited greater severity of speech deficits and axial impairments (disorders of gait and posture), which are believed to be predominantly mediated by nondopaminergic systems, also provides support for the contention that neural changes distinct from those underlying the motor disorder are likely to play a substantial role in the pathogenesis of cognitive dysfunction in PD.

This study also has some limitations. An important consideration in studies of patients with early PD concerns the accuracy of the clinical diagnosis. Clinicopathological studies indicate that, for a certain percentage of patients with clinical diagnosis of PD, the diagnosis may not be confirmed by neuropathological examination *(Hughes et al, 1992)*. Although

we cannot exclude that some patients in our sample might have been misdiagnosed, we minimized this possibility by including only patients whose diagnoses were confirmed by the neurologic examination performed as a part of the study. Furthermore, because the degree of motor disorders and cognitive impairments in our PD sample was relatively mild, it is possible that meaningful associations between cognitive functioning and motor symptoms may have been left undetected. Finally Logitudinal study in necessary to determine whether increasing disease duration exacerbates the early cognitive deficits and affects new cognitive domains, in addition to producing increasing motor disability.

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Authors:
Abo-El-Naga Y
Lecturer of Neurology
Department of Neuropsychiatry
Ain Shams University

Address of Correspondence:
Abo-El-Naga Y
Lecturer of Neurology
Department of Neuropsychiatry
Ain Shams University

Patients and Staff Attitudes toward Physical Restraint

Elgamal M

Abstract

The purpose of the study was to obtain patients and staff attitudes toward physical restraint. Also detection of different variables affects their perceptions and responses. 30 patients experienced physical restraint and 48 psychiatrist, 62 nurses who had direct contact and routinely use this technique were subjected for especially designed questionnaires for patients / staff attitude and reason opinions, delivered in both Arabic and English versions. Patients were diagnosed by DSM - IV structured interview. Demographics and clinical characteristics and restraint event are collected. Descriptive statistics, correlations and analysis of variance were used to examine patients and staff responses. The patients means ages was 33.9 ± 13.1, 3/4 were males, behavioral problems were the dominant presentation (76.7%) and mood disorder (manic episode) form 60%. More than 50% of patients had negative attitudes and not accepting restraint as away of management. Females, younger patients and those with first admission, short illness duration, and poor compliance were at high risk for negative attitude. Using force with restraint procedure significantly associated with negative responses. Helplessness, negligence, rejections, punishments, aggression and negative Thoughts, confusing emotions were the higher responses. There was high agreement between psychiatrists and nurses in most of responses, But nurses had more aggressive / harsh attitude than psychiatrist (P = 0.03) and admit more that force is the rule (P = 0.005). Nurses and patients' gender as well as level of experience and professionalism affect the nurse's response. Physiatrist demographics had no effect on their attitudes. Negative attitudes for patients and staff responses highlight. The importance of educational programs of restraint, directed for increasing sensitivity of risk group detection and gaining to decrease such negative perceptions. Needs for researches about other alternatives with of restrictive and directed for its comparative efficacy.

Introduction:

Coercive measures in psychiatry, although in many cases effective in violence management and injury reduction, have been criticized from a consumerist point of view. Soloff (1984) noted that the controversy over the legitimacy and efficacy of physical technique reflects broader social, cultural and educational perspectives.

Society currently demands that mentally ill persons be treated with the least restrictive methods and advances in psychopharmacology have allowed many severely ill patients to be managed without excessive use of restraint. However, negative side effects of many psychotropics rule out use of these medications with some patients ***(Klinge V.1994)***.

Patient attacks on healthcare personnel can have devastating effects such as workplace stress, post traumatic stress disorder or at lesser extent, physical injury. The most affected group is the nursing profession with almost 100% of nurses experiencing patient violence in the course of their career compared to 61% for other personals (***Wynn R, Bratlid T 1998)***.

Some clinical experts advocate the benefits of the interventions in preventing injury, reducing sensory stimulation, maintaining the ward milieu and conserving staff resources. Others advise continuous use of the interventions noting that they have few therapeutic benefits and may have unintended adverse effects on patients and staff (***Outlaw F, Lowery B1992)***. Others have focused on the therapeutic contraindication for use of restraint with certain populations, including persons with compromised physical health, children and elderly persons ***(Burger S 1993)***.

Generally, patients have negative feeling about being restrained. They describe feeling discomfort, anger, fear and resentment. They also indicate the event of being restrained as a memorable one that is filled with conflict and uncertainty and one they want resolved (***Miller, D. Walker, M.C., & Friedman, D1984)***.

Attitude therapy and training programs have been used successfully to help the staff to reduce the use of restraint. Understanding patient attitudes, as a part of an educational program changed the staff's use of restraint. Also, education about the nature of violence has demonstrated a change in the way staff relates and handle violent behavior (***Owen, C., Tarantello, C., et al*1998).**.

Service planning and training programs need accurate data about hospital characteristics, patients clinical and demographic data, causes and circumstances and procedures of restraint and other alternative least restrictive methods availability as well as knowing patients and staff opinions about this physical method of management.

Objectives:

1. Patients attitudes toward physical restraint.
2. Staff opinion about reasons and attitudes toward restraint.
3. Studying Demographic and clinical factors that may associated with different attitudes and opinions.

Subjects and methods

Hospital characteristics: -

The study was done at Kuwait state psychological medicine hospital. It consists of

- Eight acute wards.
- Four rehabilitation wards.
- Four forensic wards.
- Two wards for chronically institutionalized patients.

The study was performed in four acute wards (2 for male, and 2 for female inpatients), as representative for acute wards.

Subjects:

30 patients selected from male and female wards, by systemic randomization over six months from first January up to 30 June 2006.

1. Age above 15 years.
2. Both sexes.
3. Experienced physical restraint at least one on current admission.
4. Assessment after patient settled down with clinical improvement of his mental state and no more restraint.
5. Cooperative, agreement and consent obtained.

Exclusion:

1. Impaired cognitive function, consciousness that impaired patient cooperativeness.

2. Mental retardation.

3. Refusal and uncooperative ones.

4. Patients who are unable to speak Arabic or English.

Psychiatrists and nurses staff of different age, Experience, both sexes, who are indirect contact with patients assessed for the study.

Methods and Procedures: -

1. Semi-structured designed sheet to collect demographics and clinical data of patients as well as characteristics and circumstances of restraint event.

2. Patients information was collected by direct interview, file notes & nurses direct questioning.

3. Structured DSM-IV interview for clinical diagnosis.

4. Demographics of staff (gender, nationality, level of education, years of experience, Job description hierarchy.

5. Questionnaires:

- Three designed questionnaires especially by the researcher for patient's attitudes, reasons opinion, staff attitudes.

- All were delivered by direct interview of the patient and direct communication to the staff members; ensure respond to them anonymously and separately.

- Arabic as well as English version by translation & retranslation.

- The statements were simple and direct.

A. Patient attitude questionnaire: - **(Appendix 1)**

17 statements, examine different responses in (yes/no) answers. The statements were re-grouped to give general attitudes offer them individual items.

* Five attitudes were described.

1. Acceptance / welcome attitude: - including patients who respond by (yes) on statements (1, 2, 5). Agree about restraint, prefer restrain than drug, and trust their staff decision about restrain.

2. Refusal attitude: - Patient respond positively on (4, 6, 17) statements, where patients experience restrain as punishment, decide to avoid readmission because of restraint and not accept restraint as way of management.

3. Aggression release response:- Statements (3, 7, 13) where patients report that aggression is natural result of restraint, decide to breakdown hospital structure or discipline as well as homicidal tendencies.

4. Positive emotions and thoughts response: - Statements (14, 15, and 16) where patient experience support from others, sense of being strong, powerful and controllable and secure during this experience.

5. Negative emotions and thoughts response: - Statements (8, 9, 10, 11, and 12) where patients experience mixed confusing emotions, positive and negative thoughts toward others, feel negligence and rejection helplessness, admit death wishes and / or suicidal thoughts.

B- Reasons opinion questionnaire: **(Appendix 2)**

Eleven statements that describe certain issues around different indications for restraint. Staff respond in (agree disagree and uncertain way).

C- Staff attitude questionnaire: **(Appendix 3)**

16 statements which describe different attitudes of staff (psychiatrist & nurse) who had direct contact with the patients. They respond by (agree - disagree, uncertain).

These statements are describing three main attitudes.

1. Welcome / acceptance attitude:- statements number (1,5,8,11,13), where staff respond that all agitated patients should be restrained, patients had no rights to refuse restraint, prefer continuous restrain admitting physical retrain is preferable even with risk of hazardous than drugs which only added of patients not completely controlled.

2. Aggressive / harsh attitude: - statements (3, 4,7,14, 15) where staff who respond positively on these items considered with harsh / aggressive attitude on the restraint procedure (force is rule; underestimate the risk of complications, communication with patient on restraint is of no value, written order is not mandatory.

3. Conservative attitude: - Statements (2, 6, 9, 10, 12, and 16) where they keep in mind certain precautions and procedures when physical restraint is indicated.
* Written order & psychiatrist attendances are mandatory.
* Keeping watch over the patients.
* Release, patients on partial control.
* Educate the patient about indication & procedure.
* Prefer short time restraint.
* Prefer chemical restrain to avoid restraint hazardous.

Questionnaires reliability: -
By using Cronbach's alpha test the reliability was as follow.

Questionnaire name	Subjects	Subject number	Items number	Reliability by Cronbach's Alpha
1. patient attitude	Restrained patients	30	17	0.645
2. reason opinion	Psychiatrist nurse	48 62	11	0.530 0.473
3. staff attitude	Psychiatrist nurse	48 62	16	0.652 0.626

Statistical Methodology

Data were collected and coded then entered into an IBM compatible computer, using the SPSS version 12 for Windows. Entered data were checked for accuracy then for normality, using Kolmogorov-Smirnov & Shapiro-Wilk tests, and proved to be normally distributed. Qualitative variables were expressed as number and percentage while quantitative variables were expressed as median, mean ($\overline{X}$) and standard deviation (S).

The arithmetic mean ($\overline{X}$) was used as a measure of central tendency, while the standard deviation (S) was used as a measure of dispersion.

The arithmetic mean and the median were used as measures of central tendency, while the standard deviation was used as a measure of dispersion. The percent change was computed to express the change in the repeated variables as a percentage.

The following statistical tests were used:-
1- Independent samples t-test was used as a parametric test of significance for comparison between two sample means, after performing the Levene's test for equality of variances.
2- Independent samples Mann-Whitney's U-test (or Z-test) was used as a

nonparametric test of significance for comparison between two sample medians.

3- The χ^2-test (or likelihood ratio =LLR) was used as a non-parametric test of significance for comparison between the distribution of two qualitative variables.

4- The Fisher's exact test was used as a non-parametric test of significance for comparison between the distributions of two qualitative variables whenever the χ^2-test was not appropriate. It gives a p-value directly.

5- Paired samples t-test was used as a parametric test of significance for comparison between before and after values of a quantitative variable.

6- The Wilcoxon signed ranks test (Z-value) was used as a non-parametric test of significance for comparison between before and after values of a qualitative or ordinal variable, when the paired-t test was not appropriate.

7- McNemar's χ^2-test was used for paired comparison of dichotomous variables.

8- The Mann-Whitney test (Z-value) was used as a non-parametric test of significance for comparison between two samples means, when the independent t-test was not appropriate.

9- The one-way ANOVA (F-test) was used as a parametric test of significance for comparison between more than two samples means, using either Scheffe's or Tamhane's post hoc tests for paired comparison according to the results of homogeneity testing.

10- The Kruskal-Wallis test (χ^2-value) was used as a non-parametric test of significance for one-way comparison between more than two samples means, when the one-way ANOVA test was not appropriate.

11- The Pearson's correlation coefficient (r) was used as a parametric measure of the mutual relationship between two normally distributed quantitative variables.

12- The Spearman's rank correlation coefficient (r) was used as a non-parametric measure of the mutual relationship between two not-normally distributed quantitative or ordinal variables.

13- Validating parameters were calculated namely sensitivity, specificity, PPV, NPV and diagnostic accuracy for clinical presentation versus results of XXX.

Sensitivity= the ability of the test to detect those with the condition.

Specificity= the ability of the test to exclude those without the condition.

Positive predictive value (PPV) = the ability of the test to detect those with the condition among positively screenees. Negative predictive value (NPV) = the ability of the test to exclude those without the condition among negatively screenees. Diagnostic accuracy = the percentage of total agreement methods regarding of both true positives and true negatives.

Results

A- Demographics:

1. for patients (Table I)

30 patients, who experienced physical restrain, were studied their demographics showed that:

* The mean age was 33.9 $\pm$13.1.

* 73.3% (22) were males, while females represent one forth of patients.

* 90% were with Arabic nationality.

* Around half of patients were married.

* Only 6.7% were illiterate and others were educated with different grades (40% low grade, 46.7% high school and 6.7% of university degree).

2. For nurses:

The questionnaire delivered to 70 nurses, 62 nurses responded to the questionnaires regarding indications and attitude toward physical restrain where 30 of them were females, 90% (50) were working as registered nurse with nursing diploma while only 10% have high nursery school and were seniors. Around 2/3 of them were Arabian. 29 of them were working in male patients wards while 33 were working in female patients wards. The mean of experience duration was (12.06± 7.6)

3. Psychiatrist:
- 48 psychiatrists out of 65 were responded to questionnaires and their demographics were distributed as following:
- 35 of them were males.
- 30 working as registrar with (MSCs) post degree and 16 of them with higher (MD) level.
- Most of them (45) were Arabian.
- Mean of experience duration was (14.6±7.2)

B- Clinical data for patients (table 2):-

- Positive psychotic symptoms, behavioral problems (aggression, irritability, roaming & hyperactive…etc) and sleep disturbance were the most symptoms expressed by patients (53.3%, 76.7%, 40% respectively).

- 60% were diagnosed as mood disorder (manic episode), while schizophrenics represent 23.3%.

- 83.3% were with positive history of restrain and repeated admissions, where more than 1/3 of patients with more than 5 admissions.

- 29.7% with duration of illness from 10 - 20 years.

- Half of the patients were with poor compliance on treatment.

- 80% presented to the hospital admitted and brought by family, while police was the source of referral in 20% all admitted via casualty.

- Regarding restraint clinical descriptions, about 80% of patients were restrained by interrupted type with range of duration between 1 - 8 hours. The range of restrained episodes number from 1 - 5 episodes and force was associated with the restraint event in such patients.

Note: Continuous restraint operationally defined more than 8 hours (number of staff hours work / day)

C- Distribution of individuals items and main categories of attitude questionnaires:

*** Individual items responses**

1. Attitude questionnaire for Patients (figure I):

About 50% questionnaire for patients:

Abut 50% or more of patients respond on items suggestive to the negative experience to physical restraint.
- 90% experiencing mixed confusing emotions.
- 86% feel state of helplessness.
- 66% reveal that aggression is the result of physical restraint.
- 63% experience restraint as punishment.
- 60% feel negligence and rejection while restrained.
- 53% admit negative thoughts and prosecution toward others.
- 46% not accepting restraint as way of management.

*** General attitude categories:**

The data showed that the least median (1) was for acceptance and welcome attitude and the highest median (2) was for both aggression release and positive emotions and thoughts.

2. Agreement between psychiatrists and nurses responses on reasons opinion and attitude questionnaires (figure 2, 3):-

- There is no statistical significance difference with high agreement between psychiatrists and nurses in all items of reason opinion and attitude questionnaires.
- Only the statistical difference with less agreement was in few items in both questionnaires.
- Psychiatrists respond more than nurses to the following items:
- Patients with substance intoxication need physical restrain (P = 0.001).

Aggressive and homicidal patients cannot controlled only by restrain (P = 0.04).

On the other hand nurses see that patients with roaming and hyperactivity could be controlled by restraint.

This view is not shared by psychiatrists (P = 0.001), (Figure 1).

- (Figure 2) showed that there is no statistical significant difference with high agreement between psychiatrists and nurses in attitude items questionnaires except that nurses highly focus on force a rule. (P=0.001), and written order as well as doctor attendance are mandatory (P = 0.004), and also patients do noise deserve restraint (P = 0.01).

Psychiatrists respond more in that drugs may be added if patient is not completely controlled (P = 0.02).

- Regarding to the main attitude categories:

There was significant difference between psychiatrists and nurses attitude on harsh / aggressive (P = 0.03). Nurses had higher tendency to aggressive / harsh attitude in Nurses than Psychiatrists. But median score for welcome / acceptance attitude and conservative attitude are the same for the two groups with no significant difference.

Statistical correlations:

I- Patients attitude questionnaire:

1. There was significant association between patient's non acceptance for physical restraint as way of management and history of admission and / or history of restrain and behavioral disturbance. Symptom, presentation, (Table 6) Also, significant negative correlation between non acceptance and age (r = 0.4, P = 0.01), duration of illness (r = 0.50, P = 0.005) and number of admissions (r = 0.39, P = 0.03).

i.e.: older patients with longer duration, repeated admissions with history of restraint and expressed behavioral disturbance were more accepting to the physical restraint as a way of management.

In contrast, younger patients with no history of admission or restraint, short duration of illness and with no behavioral disturbance were more refusing and resistant to physical restraint as a way of management.

2. Educated patients and patients with repeated admissions and history of restraint responded significantly to the feeling of strong, power and control during restraint experience.

- Patients with history of poor compliance on treatment are experiencing more mixed confusing emotions than patients with history of satisfactory drug compliance (P = 0.02).

- Destructive thoughts (breakdown of hospital structure and discipline) emerged in the mind of educated (P = 0.006), while the patient without mood symptoms has a tendency to avoid readmission because of restraint (P = 0.01).

- Table (8) showed that there is significant association between circumstances of restrain and negative emotions and though attitude (P = 0.04).

- Patient restrained by force are more prone for feeling of helplessness, negligence & rejection, released mixed confusing emotions and feel prosecution & thinking negatively toward others (P = 0.01, 0.03, 0.001 and 0.01, respectively). However, patients restrained after their agreement feel highly support from others (P = 0.006).

- Sex is significantly associated general negative emotions and thought attitude (P = 0.04), where female patients had general negative attitude and more prone to sense of negligence and rejection (P = 0.02), while males feel positively support from others (P = 0.03).
- Other demographics such as nationality and marital status are not significantly associated with patients attitudes.
- Also, source referral, way of admission (all casualty admissions), clinical diagnosis and symptoms presentation other than mood and behavioral disturbances are not significantly associated with attitudes.
- Restraint characters such as pattern, duration, number of restrain have no effect on patient's responses.

II- Psychiatrists and nurses response correlations:

A) Psychiatrist response:

Demographics for psychiatrists had no significant associations with any response on both questionnaires including gender, job description, educational level and nationality.

B) Nurses response:

1. Male nurses and nurses work in male wards were significantly associated and responded more on welcome attitude (P = 0.01, & 0.04, respectively) and prefer continuous restrain (P = 0.009 & 0.01, respectively), while female nurses and nurse working in female wards responded significantly more on patient partially controlled deserve release (P = 0.011 & P = 0.019).

2. Nurses how are less professional respond significantly on general aggressive / harsh attitude and preferred physical restrain even with high potentials of hazards (p = 0.03 & 0.01).

3. Also, nurses with less educational level respond significantly with that force is rule on physical restraint (P = 0.005), while these with high nursery school prefer short restrain (P = 0.013).

4. Duration of experience is correlated negatively with that patient with roaming and hyperactivity could be restrained (r = 0.28, P = 0.23), where nurses with longer duration of experience do not agree about restrain for such patient who were roaming or hyperactive.

Reasons and attitude correlation:

1. Nurses with conservative general attitude respond significantly with indication of restraint for patient with suicide thought or attempt for their safety (r=0.288, P = 0.023).

2. On the other hand nurses respond with welcome and acceptance attitudes.

3. Psychiatrists with higher responses on aggressive / harsh general attitude significantly associated with responses on reasons Item.

1. Psychotic patients with acting out need restrain

(r = 0.32 P = 0.02)

2. Roaming and hyperactive patients controlled by restraint (r = 0.37 P = 0.009)

3. Patient could be restrained on his request

(r = 0.31, P = 0.03)

Results:

Table (1) Demographics for 30 patients experienced physical restraint

Item		N	%
Gender	Male	22	73.3
	Female	8	26.7
Nationality	Arab	27	90
	Non Arab	3	10
Marital status	Single	8	26.7
	Divorced	8	26.7
	Married	14	46.7
Education	Illiterate	2	6.7
	Low grade	12	40.0
	High school	14	46.7
	University	2	6.7

Age mean 33.9 SD ± 13.15 Range (17 - 76)

Table (2) Distribution of clinical data for 30 patients experienced physical restraint

Item		N	%
Gender	Mood symptoms	2	6.6
	Positive psychotic	16	53.3
	Behavioral list	23	76.7
	Sleep disturbance	12	40
	Negative symptoms	3	9.9
Clinical diagnosis	Mood disorder (mania)	18	60.0
	Schizophrenias	7	23.3
	Organic syndrome	2	6.7
	Brief	3	10
Duration of illness	1 - 10 years	19	62.7
	11 - 20 years	9	29.7
	> 20 years	2	6.6
History of admission/restrain	Positive	25	83.3
	Negative	5	16.7
Number of admission	IST admission	5	16.7
	≤ 5 admission	14	46.6
	> 5	11	36.7
Drug compliance	Poor	14	46.7
	Satisfactory	11	36.6
	Non previous III	5	16.7
Source of referral	Family	24	80
	Police	6	20

Table (3) Clinical description of restraint event for 30 patients

Strain Item		N.	%
Pattern of restrain	Interrupted	25	83.3
	Continuous	5	16.7
Duration of restrain	1 - 3 hrs	13	43.3
	4 - 8 hrs	12	40.0
	> - 8 hrs	5	16.7
Number of restrained episodes	1-5	24	80
	6-10	6	20
Circumstances & agreement	With agreement	5	16.7
	by force	25	83.3

Table (4) Distribution of general attitudes for 30 patients experienced physical restraint

	Acceptance	Refusal	Release aggression	Positive emotion/Th.	Negative emotions/Th.	Total
Median	1	1.5	2	2	1.5	8
Minimum	0	0	0	0	0	3
maximum	3	3	3	3	5	13

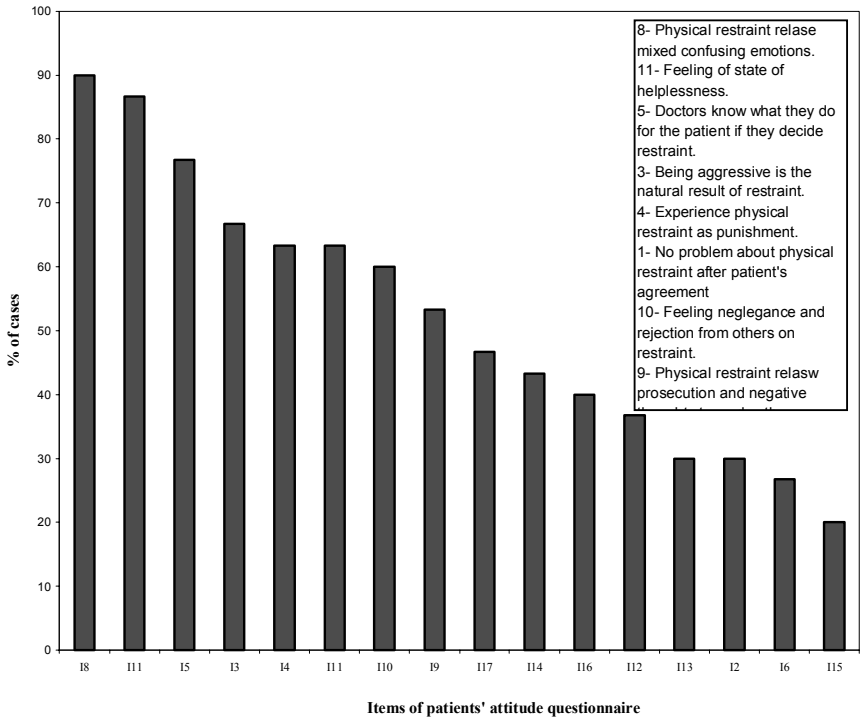

Figure 1: Rank ordered bar of statements of patients attitudes on physical restraint

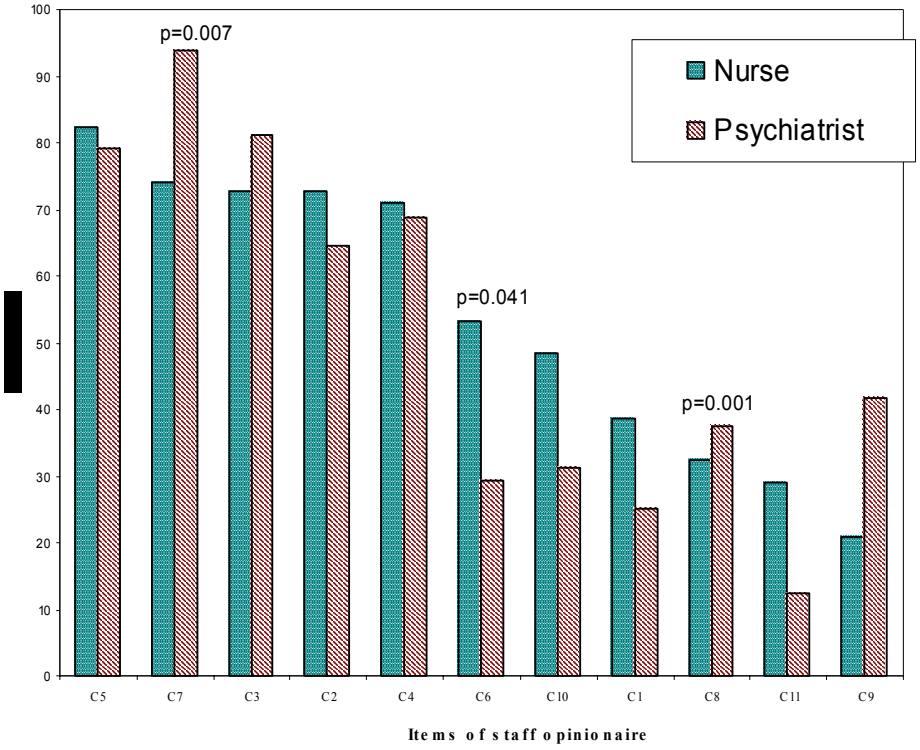

Figure 2: Distribution of the study staff according to their agreed responses regarding indications of physical restraint

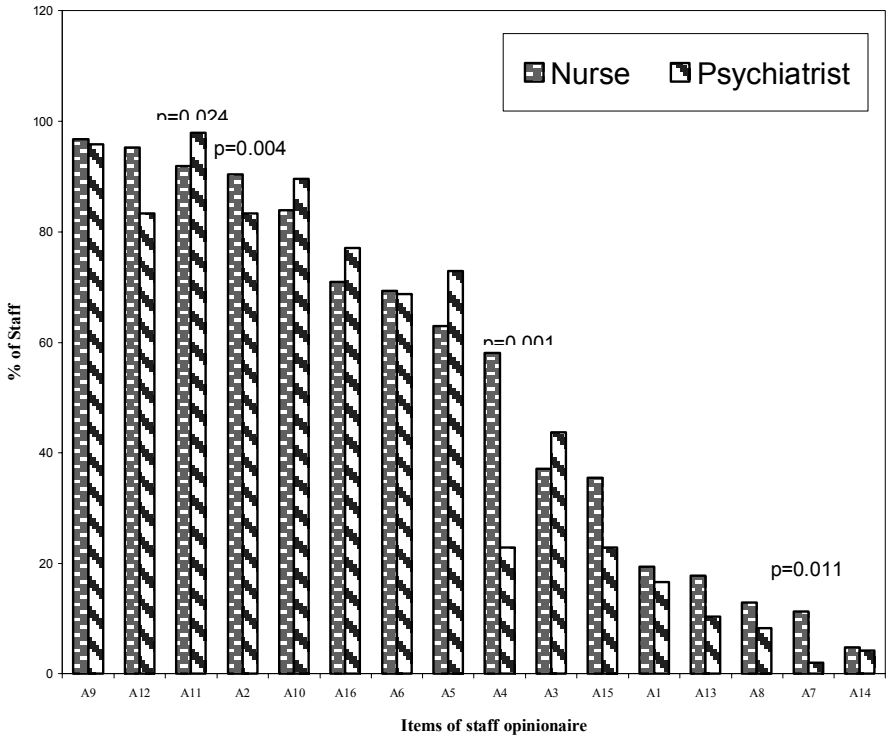

Figure 3: Distribution of the study staff according to their agreed responses regarding their attitudes about physical restraint

Table (5) Statistical correlation between different attitudes for psychiatrists and nurses toward physical restraint

Categories		Welcome	Conservative	Aggressive	Total
Psychiatrist	Min - Max	1 - 7	4 - 10	0.5	6 - 18
	Median	3	6	1.5	10
Nurses:	Min - Max	1 - 6	4 - 9	0 - 7	6 - 17
	Median	3	6	2	12
	M-W-test z	1.025	1.513	2.111*	1.623
	P	0.305	0.130	0.035	0.105

* Significant at 5% level.
** Highly significant at 1% level.

Table (6): significant associations between different attitude items and demographics as well as clinical data for 30 patients experienced physical restraint.

Attitude items	Dem/clinical data	Median	P
I am not accepting physical restraint as a way of management	Positive admission	0	
	Negative admission	1	0.02*
	Positive restrain history	0	
	Negative restrain history	1	0.01*
	With behavioral disturbance	0	
	Without behavioral disturbance	1	0.02*
During restrain I feel strong/powerful and controllable	Education		
	- illiterate	0.5	
	- educated	1	0.01*
	Positive admission	1	
	Negative admission	0	0.01*
	Positive restrain history	1	
	Negative restrain history	0	0.04*
On restrain I decide to breakdown hospital structure & discipline	Education		
	- illiterate	0	
	- educated	1	0.006**
Physical restraint release mixed confusing emotions	Drug compliance		
	Poor	1	
	Satisfactory	0	0.02*
I decide to avoid readmission by any means because of restraint	Mood symptoms		
	Present	0	
	Absent	1	0.01*

Table (7): significant association between restraint circumstances and different attitude items for patients with restraint

Attitude item	Circumstances of restraint		P
	By force	Agreement	
	Median	Median	
On restraint I feel support from others	0	1	0.006**
I feel state of helplessness	1	0	0.01*
I feel negligence & rejection from others on restraint	1	0	0.03*
Physical restraint release prosecution & negative thoughts toward others	1	0	0.01*
Physical restraint release mixed confusing emotions	1	0	0.001**
General attitude released negative emotions	1	0.5	0.04*

Table (8): significant association between sex & patients responses on restraint attitude.

Attitude item	Sex		P
	Male	Female	
	Median	Median	
On restraint I feel support from others	1	0	0.03*
I feel negligence & rejection from others on restraint	0	1	0.02*
General attitude of released negative emotions	1	2	0.04*
General attitude released negative emotions	1	0.5	0.04*

* Significance at 5% level.

** Highly significant at 1% level.

Discussion

I. Demographics and clinical characteristics:

Attempts to correlate demographics and clinical characteristics with use of restrain have failed ***(Binder, R.L.* 1979)**.

- The current study showed that psychotic, behavioral disturbance and sleep disturbance symptoms presentations and that manic episode, schizophrenia and brief psychosis were the highest diagnosis in our sample. These results are going parallel to some studies found psychosis; manic symptoms and agitation uncooperativeness, disruption of therapeutic milieu were more in patients who were restrained ***(Betemps, E.J.,* et al 1993**, ***Millstein, K.H. & Cotton, N.S* 1990** and. ***Tsemberis, S. & Sullivan, C* 1988).**

- Also, all our patients admitted via casualty and brought by family and police, these data are consistent with ***Bell, C.C. &***

Palmer, J (1983) who stated that patients who were restrained more likely to be referred to a state hospital and less likely to be referred to an outpatient setting.

- One of new results in current study is the correlations of demographics and clinical characteristics of the patients with their attitudes.

Patients who were young with first admission, short duration of illness and not exhibiting behavioral disturbance not accepting physical restraint as way of management while patients who were older, with repeated admissions, chronic course and presented with behavioral disturbance more accepting restraint.

These results raise two possibilities that acceptance or refusal of restrain for these two groups explained either by more adaptation or low rate of restrain.

The later possibility supported by different studies which denoted negative correlation of restrain use and the age ***(Oldham, J.M., et al 1983 Plutchik, R., Karasu, T.B et al 1978, Sehwab, P.J. & Lahmeyer, C.B 1979, and Tardiff, K1981).***

The first possibility may be supported from results in the current study that educated patients and patients with repeated admissions and chronic course feel positively (strong, power and control) Table (6).

II- Effect of physical restrain on Patients attitudes:

- The effect of physical restraint on patients is generally negative, where more than 50% of patients respond higher on items showed non acceptance, release aggression, feeling helplessness and mixed confusing emotions as well as sense of negligence, rejection, punishment and thought negatively toward others.

- Also, the highest median score for general attitudes were for release aggression and negative emotions and thought attitudes, while the least median score for welcome and acceptance.

These results are consistent with ***Aschen, S.R 1995, Hammill, K .et al, 1989, Heyman, E 1987, Johnson, M.E, 1998, Meehan, T., et al 2002, Norris, m.K. & Kennedy, C.W 1992 ,also Richardson, B.K 1987, Sternberg, J., Whelihan, W.,et al 1989, Tooke, S.K. & Brown, J.S, 1992, and Wells, D.A 1972)***

- Certain clinical and demographic data were statistically associated with this effect such as female gender, more educated; patients with absence of mood symptoms, using force on restrain procedures and patients with poor compliance on treatment.

In contrast, male patients and those who agree before the procedure feel support from others and patients with some education, repeated admissions and previously restrained feel strong, power and control.

The above results are unique that give light about the risk group who respond negatively with the restraint event.

Absence of correlation with other restrain characters as pattern, duration, number of episodes, way of admission, source of referral, nationality and marital status may suggest that patients response and attitude toward restrain depend more on patient gender, mental state and circumstances of restraint episode.

III Staff attitude and reason opinion:

1. There was agreement between psychiatrists and nurse staff in most of

reason opinions and attitude which reflect general conception framework toward restraint event.

2. The difference between responses in both groups reflect that nurses who are in direct contact with the patients most of times and experiencing stress. Nurses viewed that patients do noise, roaming and hyperactive deserve restrain and stress on presence of written order as well as attendance of psychiatrist and admitting that force is rule during the procedure, also scored higher on aggressive and harsh attitude than psychiatrists. This speculation may be true and constraint with conclusion that almost 100% of nurses during their carrier experiencing patient violence compared to 61% of other professionals ***(Wynn R, Bratlid T 1998)***

3. Nurses attitude and response affected by some demographics while psychiatrists attitude is not so.

A. Male nurses and nurses who work in male wards had welcome and acceptance attitude and prefer continuous restraint.

B. Nurses with less level of education have low title in job description and less duration of experience had more harsh / aggressive attitude, prefer restraint even hazardous admitting force as rule on procedure and roaming around patient controlled be restrained. On the other hand, senior nurse professionals with higher education, more experience has conservative attitude, prefer short restrain and not agree about restrain for roaming or hyperactive patients.

- Psychiatrist, who respond more in aggressive / harsh attitude see that patient with psychosis, roaming or hyperactive or request restrain should be restrained.

The above results consistent with reports that gender and level of education affect nurse staff responses and attitudes toward physical restraint ***(Klinge V 1994)***. So, nurses with less education experience and professionality are the targets of educational programs abut physical restraint.

Conclusions and Recommendations:

1. Demographics, mental state and circumstances of restraint event patients response and attitude.

2. Educational program must be directed for nurse staff of less education and experience.

3. It is critical that restraint be implemented as a last resort.

4. It is necessary to implement restraint, the decision to do so should be less arbitrary, more rational, less frequent and less traumatic.

5. Protocols and guidelines for restraint indications and procedures should be present in all centers dealing with acute psychiatric patient.

6. Educational programs for staff for detection of risk group, using alternatives with least restrictive character are valuable.

Researches directed toward prevalence and patients characteristics, hospital environment efficacy of restraint as well as educational programs on patients and staff responses.

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Authors:

Elgamal M

Appendix (1)

Patient Attitude Towards Physical

Towards Physically Restraint.

These are group of statements that give idea about your view and attitude from physical restraint as way of management.

Before this please answer the following question:-

Previous experience of Physical restraint.

* Yes ( ) * No ( )

If Yes number is: * Once ( ) * several ( )

Way of restraint:- * By Force ( ) * With Agreement ( )
* By sedation ( )

Now please answer the following by (yes) or (No):-

No	*Statements*	*Yes*	*No*
1)	No, problem about physical restraint after my agreement.		
2)	I prefer physical restraint than sleeping by drugs when agitated.		
3)	Being aggressive is natural result of physical restraint.		
4)	I experience physically restraint as punishment.		
5)	Doctors know what they do for me if they decide restraint.		

6)	I decide to avoid readmission by any means next times.		
7)	I decide to breakdown all hospital structure and discipline.		
8)	Physical restraint release confused emotions.		
9)	Prosecution & negative emotions towards others.		
10)	Negligence & rejection.		
11)	Helplessness.		
12)	Death wishes and suicidal thoughts.		
13)	Homicidal tendencies.		
14)	Support of others.		
15)	Strong, power & control.		
16)	Secure & peaceful.		
17)	I not accept physical restraint as a way of the treatment.		

Appendix (3)

Staff Attitude Towards

Physical Restraint

Dear colleague: These are group of statements about physical restraint. Please response and score for each as follow:

Agree =2 Uncertain = 1

Disagree = 0

No	Statements	Agree	Uncertain	Disagree
1)	All newly admitted patients with agitation should be restrained.			
2)	Written Order as well as doctor's attendance is mandatory.			
3)	Patients control is essential even with risk of completions from physical restraint.			
4)	Force is rule during process of physical restraint.			
5)	Patients have no rights to refuse			

	restraint when indicated.			
6)	Chemical restraint (by drugs) helps to avoid restraint hazardous.			
7)	Patients do noise deserve restrain.			
8)	Patient's control by continuous restraint is preferred than interrupted one.			
9)	I keep watch over patients with physical restraint for support and avoid complications.			
10)	Partially controlled patients deserve release.			
11)	Drugs may be added to physical restraint if patients don't controlled completely.			
12)	Education of patients about the procedures and indication of restrain is vital.			
13)	Physical restraints even with hazardous is preferable than chemical restraint by drug.			
14)	Communication with patients during restraint is of no value.			
15)	Patients may be restraint when indicated even without written order.			
16)	Short time restraint is preferred as patients feel helplessness.			

Screen For Reasons**Appendix(2)**

Of Physical Restraint.

Dear Collage, These are group of statements that indicate situations in which patients may be restraint.

Please respond to each one as follow:-

Agree =2

Uncertain =1 disagree =0

No	Statements	Agree	Uncertain	Disagree
1)	Physical restrain is better to avoid drug side effect and overdosing.			
2)	It is indicated for patients with disturbed consciousness.			
3)	Psychotic patients with acting out delusions or hallucinations could be restrained.			
4)	For safety of patients with suicidal thoughts or attempt physical restraint is indicated.			
5)	Drugs are better than physical restrain to help patient to fall into sleep.			
6)	Patients with by hyperactivity and rooming around could be controlled by physical restrain.			
7)	Aggressive or homicidal patients cannot control by physical restrain only.			
8)	Patients with substance intoxication are in need for physical restrained.			
9)	No need for physical retrain for patients showed intrusive behavior or violet the discipline of ward.			
10)	Physical restrain could be happened on patient request.			
11)	Sometimes patients could be restrained on nurse staff request without written order.			

Dear collage: Please answer the following and respond to these statements about reasons and attitude about Physical restrain as way of the management as fallow:-

Agree = 2

Uncertain = 1 Disagree = 0

Reasons of Physical Restrain	
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
Total	

Attitude towards Physical Restraint	
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
Total	

*** Years of Experience** *** Years in Hospital**

*** Position of work** *** Nationality**

*** Post degree**

المخلص العربي

رؤية واتجاه المرضي والفريق العلاجي نحو القيد البدني

[illegible]

Inflammatory Response in Schizophrenia

Sadek H.

Abstract

Schizophrenia is a devastating disorder that affects approximately 1% of the world population. It is clearly that schizophrenia is a multifactorial disorder. Numerous theories have been proposed regarding the cause of schizophrenia ranging from developmental or neurodegenerative processes or neurotransmitter abnormalities to infectious or autoimmune process. However recent investigations suggest a strong relationship between immunological effects and the pathophysiology of schizophrenia. This study was carried out to evaluate the inflammatory response in schizophrenic patients by estimating some acute phase proteins. The study included 30 patients in acute episode and 34 controls. The results denoted that most of acute phase proteins were significantly higher in patients group than controls group. It is concluded that inflammatory response is manifested in schizophrenia.

Introduction

Acute-phase response is the systemic changes that may accompany inflammation occurring distant from the site or sites of inflammation and involving many organ systems. It has been referred to as the acute-phase response (APR) even though they accompany both acute and chronic inflammatory disorders ***(Kushner, 1993)***.

Acute-phase response changes may be divided into changes in the concentrations of many plasma proteins, known as the acute-phase proteins (reactant), and occurrence of other acute phase phenomena such as behavioural, physiologic, biochemical, and nutritional changes

Acute-phase proteins are plasma proteins whose concentration increases (positive acute-phase proteins) or decreases (negative acute-phase proteins) during inflammatory response (Table 1) ***(Morley & Kushner, 1982)***.

Substantial changes in the plasma concentrations of acute-phase proteins accompany infection, trauma, surgery, burns, tissue infarction, various immunologicaly mediated inflammatory conditions, and advanced cancer. Moderate changes occur after strenuous exercise, heatstroke, and childbirth. Small changes occur after psychological stress and in several psychiatric illnesses ***(Maes et al., 1997)***.

Table 1: Acute phase reactants

Group	*Individual proteins*
positive APRs	
Major APRs	Serum amyloid A, C-reactive protein, serum amyloid P component
Complement proteins	C2, C3, C4, C5, C9, B, C1 inhibitor, C4 binding protein
Coagulation proteins	Fibrinogen, von Willebrand factor
Proteinase inhibitors	α1-antitrypsin, α1-antichemotrypsin, α2-antiplasmin, heparin cofactor II, plasminogen activator inhibitor 1
Metal binding proteins	Haptoglobin, haemopexin, ceruloplasmin, manganese superoxide dismutase
Other proteins	α1-acid glycoprotein, haeme oxygenase, mannose binding protein, leucocyte protein I, lipoprotein (a), lipopolysaccharide-binding protein
Negative APRs	Albumin, pre-albumin, transferrin, apo AI, apo AII, HS glycoprotein, inter- α-trypsin inhibitor, histidine-rich-glycoprotein

Acute-phase proteins (APP) are produced by hepatocytes when exposed to certain cytokines or hormones. Cytokines are intercellular signalling polypeptides produced by activated cells mainly macrophages and monocytes at inflammatory sites. Most cytokines have multiple sources, multiple targets, and multiple functions. The cytokines that are produced during and participate in inflammatory processes are the chief stimulators of the production of acute-phase proteins. These inflammation-associated cytokines include interleukin-6, interleukin-1b, tumour necrosis factor A, interferon, transforming growth factor b and possibly interleukin-8 ***(Wigmore et al., 1997).***

Combinations of cytokines have been found to have additive, inhibitory, or synergistic effects ***(Mackiewicz et al., 1991)***. Thus, the induction of C-reactive protein and serum amyloid A in some models requires both interleukin-6 and either interleukin-1 or tumour necrosis factor A, and the induction of fibrinogen by interleukin-6 is inhibited by interleukin-1, tumour necrosis factor a, and transforming growth factor b. Interleukin-6 enhances the effect of interleukin-1b in inducing the expression of interleukin-1–receptor antagonist, ***(Gabay, et al., 1997)*** and interleukin-4 inhibits the induction of some acute-phase proteins by other cytokines ***(Loyer, et al., 1993)*** other soluble receptors, such as those for tumour necrosis factor a and interleukin-1, are inhibitory.

Glucocorticoids generally enhance the stimulatory effects of cytokines on the production of acute-phase proteins, ***(Baumann, et al., 1987)*** whereas insulin decreases their effects on the production of some acute-phase proteins ***(Campos, et al., 1994)***.

The expression of genes for acute-phase proteins is regulated mainly at the transcriptional level, but post-transcriptional mechanisms also participate ***(Jiang, et al., 1995)***. APRs have a wide range of activities that contribute to host defence: they can directly neutralize inflammatory agents, help to minimize the extent of local tissue damage, as well as participate in tissue repair and regeneration. There is a rapid increase in the plasma concentration of many complement cascade components, the activation of which ultimately results in the local accumulation of neutrophils, macrophages and plasma proteins. These participate in the killing of infectious agents, the clearance of foreign and host cellular debris, and the repair of damaged tissue. Coagulation components, such as fibrinogen, play an essential role in promoting wound healing. Proteinase inhibitors neutralize the lysosomal proteases released following the infiltration of activated neutrophils and macrophages, thus controlling the activity of the proinflammatory enzyme cascades. The increased plasma levels of some metal-binding proteins help prevent iron loss during infection and injury, also minimizing the level of haem iron avaible for uptake by bacteria and acting as scavenger for potentially damaging oxygen free radicals.

The major APRs include serum amyloid A (SAA) and either C-reactive protein (CRP) or serum amyloid P component SAP. Ironically the activities of these three are among the least well-known. Nevertheless, their interactions with other well-defined defence systems and the magnitude and rapidity of their induction following an acute phase stimulus, together with their short half-lives, suggest a particularly critical requirement for these proteins very early in the establishment of host defence.

Significantly, individuals unable to synthesize these proteins have not been described; these major APRs are therefore likely to be of considerable clinical importance.

Fever is representative of the neuroendocrine changes that characterize the acute-phase response. Although several cytokines may induce fever, interleukin-6 produced in the brain stem is required for the final steps leading to fever ***(Dinarello, 1997)***.

Other neuroendocrine changes reflect complex interactions among cytokines, the hypothalamic–pituitary–adrenal axis, and other components of the neuroendocrine system ***(Chrousos, 1995)***. For example, inflammation-associated cytokines stimulate the production of corticotropin-releasing hormone, with consequent stimulation of corticotropin and cortisol production, and also directly stimulate the adrenal gland. Stimulation of the production of arginine vasopressin by interleukin-6 can explain the hyponatremia that occurs during some inflammatory disorders. The behavioral changes that often accompany inflammation, including anorexia, somnolence, and lethargy, are similarly induced by cytokines. Neural mechanisms have also been implicated in anorexia ***(Sarraf, et al., 1997)***. Inflammation-associated cytokines have been implicated in the pathogenesis of anemia in chronic disease; thrombocytosis, cachexia, and impaired growth in children with chronic inflammatory conditions ***(De Benedetti, et al., 1997)***.

Recently an acute phase response has been reported in schizophrenia which is clearly a multifactorial disorder that must be considered from several perspectives. From the disease perspective, two central questions concern the pathogenesis and the pathophysiology of the illness ***(McHugh and Slavney, 1998)***. In terms of pathogenesis, what are the specific genetic and environmental factors that contribute to illness risk, and how do they act in combination to produce the biochemical and structural brain abnormalities that are characteristic of illness?. In terms of pathophysiology, how do these abnormalities alter brain function in order to give rise to the clinical syndrome that we recognize as schizophrenia?. Viewed from this perspective, unravelling the pathogenesis of schizophrenia is critical for the discovery of means of prevention and deciphering the pathophysiology of schizophrenia is essential for the identification of novel targets for therapeutic intervention ***(Muller et al., 2000)***.

Currently the problem of the aetiology of schizophrenia remains unsolved. The search? for the cause of this illness or group of illnesses has covered many areas of enquiry and we do not know how close we are to a fruitful approach.

The involvement of immunological and immunopathological mechanisms in the etiopathogenesis of schizophrenia has been a matter of research with recently increasing efforts ***(Lewis & Levitt 2002)***. Some data suggest an autoimmune component in schizophrenia and they are consistent with brain abnormalities of oligodendrocytes and myelinated fibres reported in the disease ***(Karry, et al., 2004)***.

So our aim in this study was to measure some acute phase proteins in cases of untreated schizophrenic patients to examine if acute phase response is present or not in a trial to unravel part of the secrets of etiopathogenesis of schizophrenia.

Subjects & Methods

The study was conducted at the institute of Psychiatry, Ain Shams University within the period of one year; the study included 30 patients & 34 healthy controls. The group of patients was further subdivided into 2 groups: group A including 18 patients with 1st episode of acute schizophrenia and group B including 12 patients in relapse after stopping treatment for at least 3 months.

- (1st episode: 2 weeks up to 6 month of presentation)
- (Relapse: 3 days up to 6 month of presentation)

Subjects:

A- Patient Group

Inclusion Criteria:

1. Out patients at the institute of Psychiatry
2. Never been treated in relapse and not receiving any treatments to the past 6 weeks.
3. Age between 22 and 50
4. Sex: both males and females
5. Fulfilling the criteria for diagnosis of Schizophrenia according to the ICD-10 diagnostic criteria for research.

Exclusion Criteria:

1. Presence having other psychiatric illness
2. Organic mental disorders
3. patients with substance abuse
4. Patients having symptoms and signs inflammation, infection or autoimmune disease.
5. Pregnant females or during menstruation or females on contraceptive pills.
6. Patients on steroid therapy or receiving contraceptive pills.
7. Patients with liver diseases, pancreatitis, Nephrotic Syndrome, or biliary obstruction.

B- Control group:

1. Normal individuals matched to age, sex, and other demographic variables of the patient group.
2. Physical illness was excluded by complete check-up lab investigations including complete blood count (CBC), liver function tests and kidney function tests.
3. Psychiatric morbidity was assessed by General Health Questioner ***(Goldberg & Williams 1998)***

Informed consent was taken from both controls and patients.

Methods:

A- Patient Group

The patients were diagnosed according to ICD-10 diagnostic criteria for research using the schedule to clinical assessment in neuropsychiatry (SCAN), ***(Abou Raya, 1998)***. Patients were not on medications or ECT for at least 6 weeks.

B- Control group:

The control group was subjected to the General Health Questioner ***(Goldeberg, 1998).*** The scale of 28 items was used in the Arabic version ***(Okasha et al., 1998)*** to exclude any mental disorders.

Sample Collection:

For each patient of control, 10 ml of blood were collected using routine venipuncture recautions, blood was divided into 3 parts:

1. Six ml collected blood o assay: ALT, AST, total proteins, urea creatinine, albumin, bilirubin and acute phase proteins:C3, C4, α1AT, α1glyc., HP and C-reactive protein.
2. Two ml. on EDTA for CBC

3. Two ml. anticoagulated with citrate 1:9 to estimate fibrinogen level in plasma.

All samples were transported to the lab within half an hour to be separated and stored at -20 C to be assayed within two weeks except for the CBC, ALT, AST, total proteins, albumin, bilirubin, urea and creatinine were estimated immediately. α1AT, HP, α1glyc., 3 and C4 were estimated by Radial Immune Diffusion technique (RID) using Bioscientifica S.A. plates. The diameter of the precipitation ring is measured by a magnifying glass lens and the results were evaluated by using tables of standard curves ***(Berne, 1974)***.

- CRP was detected by latex (Avitex) from omega diagnostics where latex suspension coated with serum; clear agglutination is seen in positive cases within 2 minutes. Serial dilutions were performed to estimate the titre.
- Fibrinogen was assayed by Hemosta fibrinogen (Human) using fibrin timer where thrombin is added to a pre-diluted plasma sample, the measured clotting time is inversely proportional to the fibrinogen concentration in specimen (Claus 1957) the clotting time is blotted on a calibration curve to estimated fibrinogen concentration.

Results

In our study, there was no significant difference between patient and control groups as regards the age and gender. The mean age for patients was 34.46 years while that of the controls was 33.64 years. Out of total 30 schizophrenic patients there was 8 females and 32 males, while in the control group out of 34 normal subjects there was 8 female and 26 males (Table 1).

The group of patients was further subdivided into 2 groups: group A including 18 patients with 1st episode of acute schizophrenia and group B including 12 patients in relapse after stopping treatment for at least 3 months (Table 5) (Figure 1):

Comparison of acute phase proteins between patients and controls (Table 2) (Figure 2):

Compliment 3 (C_3)

Comparing the mean value of C_3 in the patient group, it was 158.94 ± 94.9 mg/dl while it was 124.86 ± 50.6 mg/dl in the control group with a significant difference between the 2 groups ($p < 0.05$).

Compliment 4 (C_4)

As regards serum concentration of C_4, the mean value of the patient group was 39.53±21.2mg/dl and 28.92 ± 12.6 mg/dl in the control group with a significant difference between the 2 groups ($p < 0.05$).

Alpha1 Antitrypsin (α1AT)

The mean value of α1AT of the patient group was 104.5 ± 52.5 mg/dl while it was 120.81± 64.6 mg/dl in the control group with no significant difference between the 2 groups ($p >0.05$).

Haptoglobin (HP)

Regarding serum concentration of Haptoglobin there was a significant difference between the patient group and control group as the mean value of patient group was 158.95 ±124.8 mg/dl while that of the control group was 94.59 ± 60.1 mg/dl ($p <0.05$).

Alpha1 acidglycoprotein (α1glyc)

There was a highly significant difference in the mean value of α1glyc. of the patient group 196.40 ±117.4 mg/dl and control group 123.74 ± 59.5 mg/dl ($p <0.01$).

Fibrinogen (Fib)

Comparing fibrinogen level of the 2 groups, mean value of fibrinogen of the patient group was 280.80 ± 93.1 mg/dl while it was 242.18 ± 48.3 mg/dl of the control group with a significant difference ($p < 0.05$).

C- reactive protein (CRP)

Qualitative estimation of CRP showed that serum of all patients and control were negative for CRP with no difference between the 2 groups (Table 3).

When comparing the group of 1st episode and that of relapse, there was no significant difference in the acute phase proteins levels of the 2 subgroups (Table 4).

Table 2: Cases & Controls Distribution By Gender

Subjects	CASES		CONTROLS	
	No	%	No	%
Female	8	26.7	8	23.5
Male	22	73.3	26	76.5
Total	30	100	34	100

Table 3: Comparison of CRP in Patients & Controls

CASES		CONTROLS	
No	CRP	No	CRP
30	Negative	34	negative

Table 5: Frequency of 1st Episode Cases & Controls

	Schizophrenic Patients	
Patients	No	%
1st Episode	18	60
Relapse	12	40
Total	30	100

Table 2: Comparison of the Mean Level of Acute Phase Proteins between Schizophrenic Patients & Controls

APP	CASES			CONTROLS			t	P
	No	Range	Mean ±SD	No	Range	Mean ±SD		
C3	30	52.9-348.6	158.9±94.9	34	36.0-214.1	124.9±50.6	2.0	<0.05 S
C4	30	15.1-72.4	39.5±21.2	34	4.6-53.8	28.9±12.6	2.4	<0.05 S
HP	30	28.7-451.9	158.3±124.8	34	7.5-228.7	94.6±60.1	2.6	<0.05 S
α_1AT	30	52.0-222.9	104.5±52.4	34	15.0-252.9	120.8±64.6	1.0	>0.05 NS
α_1GLYC	30	37.4-500.0	196.4±117.4	34	39.4-243.5	123.7±59.5	3.1	<0.01 HS
FIBR	30	130.0-500.0	280.8±93.0	34	147.0-355.0	242.0±48.3	2.1	<0.05 S

Table 4: Acute Phase Proteins in Cases of 1st Episode versus Relapse

APP	1st Episode (n: 18) Mean ± SD	Relapse (n: 12) Mean ± SD	T	P
C3	177.5±97	131±88	1.3	>0.05 **NS**
C4	45.18±20	31±20.8	1.8	>0.05 **NS**
HP	168.6±140	142.8±90	0.5	>0.05 **NS**
α_1AT	106.9±65.5	99.2±23.8	0.5	>0.05 **NS**
α_1GLYC	223.2±114.6	114.3±114.3	1.5	>0.05 **NS**
FIBR	274±68.9	291±123.7	0.4	>0.05 **NS**

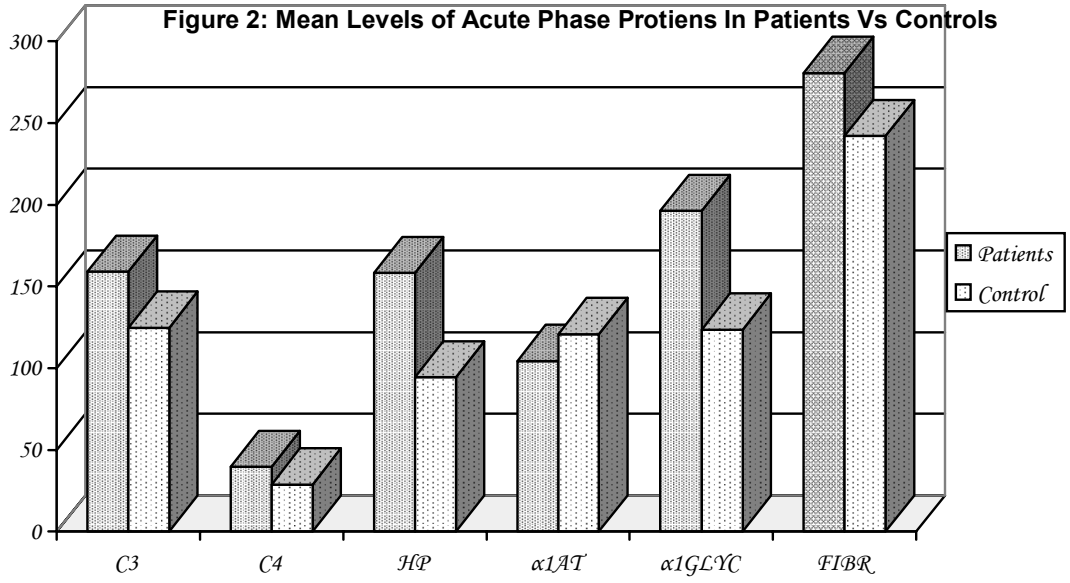
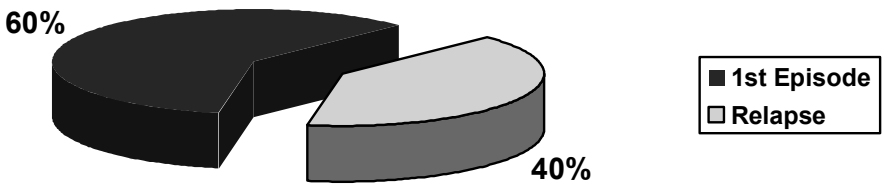


Figure 1: Distribution of Cases of 1st Episode & Relapse



Discussion

Immunological alterations have been described in the international literature since the beginning of this century. However, for several reasons the focus of interest turned away from the immune system. One reason was the introduction of neuroleptics into the therapy of schizophrenia leading to the dopamine hypothesis as the centre of research activities. Another reason was that the components and functions of the immune system have not been understood very well during those times. Schizophrenia is a heterogeneous disorder as regards the clinical symptomatology, the acuity of the symptoms, the course, the treatment response and probably also the etiology. A widespread heterogeneity can also be observed in the results of immunological studies in schizophrenia. However recent investigations suggest a strong relationship between immunological effects and the pathophysiology of schizophrenia ***(Müller et al., 2001)***.

The present study was undertaken to evaluate the acute phase response in schizophrenic patients as compared to normal controls by estimating some acute phase proteins in both groups. The acute phase proteins that have been studied are C3, C4, HP, α1AT, α1glyc., fibrinogen and C-reactive protein.

Our results denote that most of APP (C3, C4, HP, α1glyc. and fibrinogen) were significantly higher in patient group than the control group. In contrast, α1 AT showed no significant difference between the two groups.

This was in agreement with the study of Maes et al. 1997 who examined AP response in 27 schizophrenic, 23 manic, 29 major depressed and 21 normal subjects by measuring haptoglobin (Hp), immunoglobulin G (IgG), IgM, fibrinogen (Fb), complement component 3 (C3C), C4, α_1-antitrypsin (α_1AT), α_1-acid-glycoprotein (α_1S) and hemopexin (Hpx),. Schizophrenic patients had significantly higher plasma Hp,

Fb, C3C, C4, α_1S and Hpx than normal controls. Manic subjects showed significantly higher plasma Hp, Fb, α_1S and Hpx than normal controls. Depressed subjects had significantly higher plasma Hp, Fb, C3C, C4 and α_1S than normal controls. Overall, the above disorders in AP reactants were more pronounced in schizophrenic than in depressed subjects. They suggest that not only major depression but also schizophrenia and mania are accompanied by an AP response, and that the latter may be suppressed by chronic treatment with antipsychotic drugs.

In contrast to the study of Mazzarello et al. 2004 who reported increased s CRP in schizophrenic patients; there was no difference in CRP between schizophrenic patients and controls in our study. However elevated s levels of CRP may be associated with more severe psychopathology in a subgroup of patients with schizophrenia ***(Fan et al., 2007)***.

The difference between the results of our study and other studies as regards CRP may be due to the use of qualitative method for estimation and limited number of cases. Wan et al. 2007 focused on detecting schizophrenia related changes of plasma proteins using proteomic technology and examining the relation between schizophrenia and haptoglobin genotype. They investigated plasma proteins from schizophrenic subjects and healthy controls by two-dimensional gel electrophoresis (2-DE) in combination with mass spectrometry. To further reveal the genetic relationship between acute phase proteins and schizophrenia disease, they tested Hp α1/Hp α2 polymorphism and two single nucleotide polymorphisms of Hp. They found that four proteins in the family of positive APPs were all up regulated in patients and significant associations existing between schizophrenia and Hp polymorphisms. Schizophrenia is accompanied by both an altered expression of Hp protein and a different genotype distribution of Hp gene, demonstrating that Hp is associated with schizophrenia. Results indicate that acute phase reaction is likely to be an aetiological agent in the pathophysiology of schizophrenia, but not just an accompanying symptom.

In a previous study on Egyptian non paranoid schizophrenic patients, there was no significant difference in C3,CRP,α1 AT and ESR between patients and the controls ***(Okasha et al., 2006)***. They agreed with our study as regards CRP and α1 AT. However, the difference in C3 results may be due to different subgroup of schizophrenic and limited numbers of patients of the previous studies.

Conclusion

We concluded that inflammatory response is a series of immunological changes that are manifested in schizophrenia. It is reflected by the increase in the serum level of some positive acute phase proteins: C3, C4, α1 acid glycoprotein, fibrinogen and Haptoglobin.

Recommendations:

- Study of acute phase proteins in response to treatment.
- Study of other immune parameters in schizophrenia.
- Study the relation of acute phase proteins with different types of schizophrenia and the severity of illness.

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Author

Sadek H.
Lecturer of Psychiatry
Institute of Psychiatry
Ain Shams University

Address of Correspondence

Sadek H.
Lecturer of Psychiatry
Institute of Psychiatry
Ain Shams University

Psychosocial aspects of end stage renal disease Cognitive and emotional changes in pre renal and post renal transplants recipients

El Taweel M. and Ali H

Abstract

Recent studies have shown a high prevalence of depression and cognitive changes in patients with end stage renal (ESRD) adrenal transplant recipients. There are few data available on the cognitive and emotional changes in patients undergoing renal transplantation .The aim of this study was to evaluate the changes cognitive profile and depression in renal transplant recipient s .Thirty consecutive patients undergoing renal transplantation were evaluated one month before and three months after successful renal transplant with Beck Depression Inventory (BDI) ,Luria Nebraska Neuropsychological Battery (LNNB) ,Wechsler Performance Intelligence Scale (WAPIS) and life satisfaction scale . Our study revealed an 86.6 % prevalence of depression in ESRD patients as compared to 56.6% in post renal transplant patients. Analysis of neurocognitive functions on LNNB did not reveal any significant improvement .Furthermore, analysis of life satisfaction scale revealed most of the patients showed high satisfaction levels despite the stress of their disease. Results on WAPIS showed significant improvement in intelligent quotient (IQ) after renal transplantation. Successful renal transplant is associated with improvement in depression and life satisfaction.

Introduction

The incidence of renal failure is about 200 in a million people each year. Most of the illnesses causing renal failure are not in older people , but usually in young adults .Dialysis and kidney transplantation are the two basic treatments for chronic renal failure .Peritoneal dialysis and haemodialysis are the two main forms of dialysis. Haemodialysis is the preferred option used by most centers Haemodialysis imposed severe restrictions on the patient and family The patient is placed in a situation that he is totally dependent on a machine and medical personnel two or three times a week . He needs a strict diet and multiple daily medications. Water intake is restricted to a small piece of ice. The cost of the treatment is prohibitive and the loss of working days treatment adds to the financial stress .Depressed mood and depressive syndromes are common occurrences in these patients. (Barisic et al. 2004).This is understandable since depression commonly follow loss and these patients lose their independence , strength job and energy .The evaluation of depression is complicated by the fact that the symptoms end renal disease (ESRD) such as diminished appetite , loss of energy constipation and diminished sexual ability resemble the somatic symptoms of depression. Presence of anhedonia , poor self esteem , crying spells , helplessness , and suicidal ideation are indicators of the disease .Organic brain syndromes such delirium and dementia are common in these patients .Patients involved in intellectual work noticed progressive impairment in their intellectual abilities as the day of dialysis approaches . (Banies LS,

Jindal RM 2002 and Levy NB Cohen 2001).

A successful transplant dramatically improves the quality of life of the patient. The patient is free from dependence on a machine, dietary restriction and loss of workdays due to dialysis. Cognitive function is said to improve and in children growth and development regains normal levels. (Kramer et al 1996).

Transplantation has its own problems. The patients are on lifelong immunosuppressant such as steroids, which have their own side effects. The fear of rejection looms large and the patient still has to under regular medical supervision. Some workers have not found any difference between transplanted patients and those on dialysis on measures of psychological adjustment and vocational rehabilitation ((Fallon et al., 1997).

In view of the contradictory findings and paucity of kuwaitian studies in this field, the present study was undertaken to find out the prevalence of depressive symptoms, cognitive function and life satisfaction in haemodialysis patients and to assess the changes in these parameters following a successful renal transplant.

Methods

All patients with ESRD admitted to Hamd EL Essa Organ Transplantation Center in Kuwait and being worked –up for renal transplantation were included in the study. The patients (n=30) had been on regular haemodialysis for at least 6 months.

Inclusion criteria

- Patients diagnosed as ESRD who were on regular dialysis and were awaiting surgery.

- Age more than 18 years and less than 60 years.

Exclusion criteria

-Age less than 18 and more than 60 years.

-Coexisting medical illnesses such as ischaemic heart disease (IHD), diabetes, asthma, hepatitis, coexisting infections and head injuries.

-Past or family history of psychiatric disorders.

After selections and before administration of the tests an informed consent was taken from the patients. All patients were evaluated 1 month before undergoing transplantation and 3 months after renal transplantation.

All patients were subjected 1 month before and 3 months after renal transplantation to the followings;

-Beck Depression Inventory (BDI)

-Luria Nebraska Neuropsychological Battery (LNNB)

-Weschler Adult Performance Intelligence Scale (WAPIS).

-Life Satisfaction scale.

The tests were administered in more than one session to avoid exhaustion and boredom in the patients. The tests were scored as per the test booklet .The results were tabulated and analyzed using SPSS software.

Results

Table (1) Sample catachrestic

Sex	No (%)
Male	28 (%)
Female	2 (6.7%)
Mean Age	39.6
Education	
Intermediate	14 (46.7)
Secondary or Higher	16 (53.3%)
Married	26 (86.7)

The mean age of the ESRD was 39.6 years. There were 28 males and 2 female patients.

Table (2)

BDI score	**Pre-transplant**	**Post-transplant**
Not depressed (O-9)	4(13.3%)	13(43.3%)
MILDLY DEPRESSED(10-16)	8(26.6%)	17 (56.7%)
Moderately depressed (17-29)	10(33.3%)	0
Severely depressed (more than 29)	8(26.7%)	0
Mean score	22.03	9.83**
Cognitive affective BDI	15.01	4.68
Somatic BDI	7.02	5.15

**p (0.01 highly significant (wilcoxonsing rank test)

Shows that 86.7% of the pre –transplant cases were depressed (score ` 9 on BDI) and this fell to 56.7 % after transplantation. An important finding was that 69% of the pretransplant cases were moderately to severely depressed while none of patients were moderately to severely depressed after renal transplant .The average BDI score was 22.03 in this population and the score decreased significantly to 9.83 following renal transplantation. We also subdivided the BDI score into cognitive affective components taking the first 13 statements, which is said to be a more accurate measure of depressive symptoms in physically ill patients .The average score on the cognitive scale was 15.01 and this reduced to 4.68 after transplant, while the somatic score reduced from 6.02 to 5.15 underlying the fact that the effect of renal transplant was mainly on the cognitive affective component of BDI.

Table (3)

Description	Pre-transplant	Post-transplant
	N(%)	N(%)
Feelings of punishment	17(56.7)	10(33.03)
2-Self-critical	13(43.3)	8(26.7)
3-Crying spells	13(43.3)	5(16.7)
4-Worthlesness	12(40.0)	2(6.7)
5-Loss of energy	12(40.0)	6(20.0)
6-Indecisiveness	10(33.3)	2(6.7)
7-Sense of failure	10(33.3)	11(37.3)
8-Sadness	8(26.7)	1(3.3)
9-Pessimism	6(26.7)	4(13.3)
10-Sleep disturbance	8(26.7)	4(13.3)
11-Irritability	8(26.7(	7(23.3)
12-Fatiguability	8(26.7)	8(26.7)
13-Loss of pleasure	7(23.3)	3(10)
14-Loss of interest	6(20.0)	5(16.7)
15-Self-hate	5(16.7)	5(16.7)
16-Difficulty in concentration	5(16.7)	3(10.0)
17-Guilty feelings	3(10.0)	1(3.3)
18-Agitation	2(6.7)	2(6.7)
19-Loss of appetite	2(6.7)	1(3.3)
20-Loss of libido	1(3.3)	1(3.3)
21-Suicidal thoughts	0 (0.00)	0(0.00)

Showed that in ESRD patients cognitive affective symptoms such as feelings of punishment, crying, being self critical, indecisiveness, past failure, and worthlessness were common. Among the somatic symptoms, loss of energy was a common symptom. Suicidal ideation was not present in any patient. Post transplant, the sense of failure showed a mild increase, but all the other symptoms either decreased or remained the same.

Table: (4)

WAPIS scoring	Pre-transplant	Post-transplant
Mean IQ	88.5	101*
Bright –normal (110-119)	0(0%)	2(6.7%)
Average (85-109)	22(73.3%)	28(93.3%)
Borderline (70-84)	8(26.7%)	0(0%)

*p less than 0.05 significant (Wilcoxon sign rank test).

On the WAPIS, there was a highly significant increase in mean IQ scores after renal transplant (table 4). Before transplant, 22 patients were in the average range for intelligence and 8 showed borderline retardation. After transplant, 2 moved to the bright normal range while all borderline retardation patients moved to the average range, thus indicating that this disease affects the intelligence.

Table 5

WAPIS subtest	Pre-transplant	Post-transplant
Picture completion	7.40	9.87*
Digit symbol	8.77	11.27*
Block design	7.37	9.43*
Picture arrangement	8.83	9.90*
Object assembly	9.20	10.47*

*p less than 0.05 significant

A significant difference was also observed between pre- and post-renal transplant cases in all the subscales of the WAPIS.

Table 6

BDI scoring		WAPIS subtest				
	Picture completion	Digit symbol	Block design	Picture arrangement	Object assembly	IQ performance
Pre-renal transplant	-0.406 0.026*	-0.202 0.285	-0.242 0.117	-0.061 0.750	0.191 0.311	-0.195 0.302
Post-renal transplant	-0.o60 0.753	-0.247 0.189	-0.388 0.034*	-0.005 0.977	0.036 0.849	-0.254 0.175

Pearson Correlation significant (2-tailed indicating significance at 0.05 level)-

The BDI scores of the ESRD patients did not correlate with performance IQ except in the picture completion test. After renal transplant, again the BDI scores did correlate with the performance IQ except the block design test. This indicates that the lower IQ seen in the patients before renal transplant was not due to the effect of the depression as measured by the BDI.

Table 7

Clinical scale	Mean scoring	
	Pre-transplant	Post-transplant
1-Motor function	35.43	31.50**
2-Intellectual functions	30.35	34.23*
3-Expressive speech	40.10	33.77**
4-Receptivel	40.90	35.87**
5-Visuale	38.77	33.33*
6-Tactile	41.83	39.30
7-Reading	49.10	40.37*
8-Writing	42.33	40.93
9-Arithmetic	46.43	45.93
10-Memory	38.57	34.90*

*p less than 0.05 significant **p less than 0.01 highly significant

On the LNNB, significant differences were seen in motor functions, intellectual functions, receptive speech, expressive speech, visual functions. Reading and memory following renal transplant.

Table 8

LNNB clinical scale	Pre-transplant		Post-transplant	
IQ	BDI scoring	IQ	BDI scoring	IQ
-0.222 0.238	-0.264 0.159	-0.097 0.612	-0.264 0.159	-0.097 0.612
-0.144 0.448	-0.325 0.880	0.088 0.645	-0.325 0.880	0.088 0.645
-0.019 0.922	-0.160 0.397	0.355 0.054	-0.160 0.397	0.355 0.054
-0.108 0.571	0.095 0.615	0.132 0.487	0.095 0.615	0.132 0.487
-0.024 0.897	-0.486 0.006	0.391 0.032	-0.486 0.006	0.391 0.032
-0.222 0.239	0.054 0.778	0.021 0.914	0.054 0.778	0.021 0.914
-0.267 0.154	-0.041 0.832	0.150 0.429	-0.041 0.832	0.150 0.429
-0.198 0.295	-0.163 0.389	-0.024 0.899	-0.163 0.389	-0.024 0.899
-0.028 0.882	-0.116 0.542	0.169 0.372	-0.116 0.542	0.169 0.372
0.061 0.750	-0.070 0.713	-0.117 0.536	-0.070 0.713	-0.117 0.536

Pearson Correlation (2-tailed) between BDI and IQ with LNNB clinical scales .

There was no correlation between BDI and IQ with LNNB clinical subscales in the patients before and after renal transplant.

Table 9

Life Satisfaction scale scoring	Pre renal-transplant	Post renal-transplant
High score	15	30
Average score	15	0
Mean score	133	153*

*p less than 0.05 significant

On the life satisfaction scale, 15 patients scored in the high range and 15 in the average range before renal transplant All patients in the average group shifted to the high satisfaction group postransplant. There was also a significant rise in the mean life satisfaction score after renal transplantation.

Discussion

ESRD is a psychologically debilitating disease with considerable emotional morbidity. Depression is the most common symptom in these cases and has been attributed to the loss of many factors; the loss of independence; loss of working ability .loss of healthy self image and loss or diminution of sexual ability. (Barisic et al.2004 and Knight et al. 2003).

In this study, depression was present in as many as 86.7 % of the total population before transplant (table 2), the average score being (22.03) and decreasing to 9.83 after transplantation. Taking a cut-off of 17 to obviate the effects of symptoms due to the illness from impinging on the BDI score, 60 % of the population scored above the cut-off, indicating moderate to severe depression on the BDI before transplant. Similarly, a study of 62 Korean patients (Koo et al .2003) ،on chronic haemodialysis reported a 56.5 % prevalence of depression following a cut-off of above 21. In their study, 34 out of 40 patients scoring more than 18 on BDI met the criteria for major depression. However, in our study none of the patients after renal transplant had a BDI score more than 17. This is unusual as others have reported contrary findings (Baines LS Jindal RM 2002).

Teran-Escandon et al. (Teran –Escandon et al. 2001) reported as 40% prevalence of depression in their sample of post –transplant cases observed after one year. They also observed that patients who had received a kidney from live related donors had a lesser prevalence of depression than those who had received a kidney from cadavers. They hypothesized that patients with kidneys from live related donors might overestimate their prognosis. In our sample, all the patients had received kidney from a live related. Also, the patients in this study were evaluated three months after transplant, thus excluding cases of graft rejection,. This may have led to a significant improvement in the symptoms of depression in the present study. The BDI proved to be a sensitive indicator for revealing depression and detecting the symptoms in a majority of cases. Out of the total population of 30 cases, only 2 cases had been suspected of having depression by the treating nephrologists and sent for psychiatric evaluation.

The reason for this could be that are reluctant to reveal psychological symptoms to the treating doctor unless these are specifically asked for. Depression has been thought to influence the nutritional status as indicated by albumin levels, Thus, poor nutritional status may mediate the relation between depression and mortality in ESRD (Friend et al .1997). Depression in our study was not linked to diet of the patient but was significantly linked to the educational level.

An analysis of the BDI subscales reveals that punishment feelings, guilty feelings, loss of energy, worthlessness, and indecisiveness were the most common symptoms in ESRD patients. This substantiates the commonly held cultural belief that disease is a response to punishment for wrongs committed earlier. Except for the loss of energy, which may be a symptom of the disease, other symptoms are psychological thus substantiating the validity of the BDI in these cases. Sexual difficulties have been reported to be common in these cases; however, in our study only 3.7% of the cases reported sexual problems in our setting. The common symptoms in the post –renal

transplant group as reflected in the BDI were past failure, punishment feelings, crying and being self critical. These symptoms also substantially validate the effectiveness of the BDI as a tool for assessing depression in these cases. The high prevalence of depression in the pre – as well as the post –renal transplant cases may indicate the need for starting a prophylactic antidepressant in these cases. (Kramer et al.1997).

Also found a 44% prevalence of depression in patients with ESRD, which is in agreement with our findings. Their study also linked depression to increased mortality which was not able to verify. Depression is also reported to be higher men sub and linked to depression in the spouse. We unable to verify this in our study .OF the patients 26.7% had a borderline IQ before renal transplant, while after transplant none of the patients had a borderline .AIQ .To negate the influence of culture and education measured only the performance IQ using WAIPS.In a study of adults with ESRD since childhood (Groothoff et al. 2002) the performance was found to be 9.2 points lower than a comparative group of adults without renal disease. The lowest scores were observed in tasks that required concentration, memory, and general knowledge. On analyzing the subscales of WAPIS, in this study we found that the lowest scores were obtained in picture completion and block design. Picture completion is a measure of visual concentration and a non-verbal test of general information. A low score on this test may indicate difficulty in concentration and inadequate visual organization. Block design, on the other hand is said to be a relatively non-verbal culture free test of intelligence which correlates highly with general intelligence. It is also said to be an excellent indicator of brain damage especially of the right hemisphere (Lezak 1996).Low scores were obtained on other subtests as well which improved significantly after transplantation .In a similar study of 9 medically stable children and adolescent, improvement in intellectual functions was found after successful renal transplant (Mendley SR AND Zelko FA 1999).In another study involving 20 children and adolescent with ESRD before and after transplantation, patients exhibited significantly greater improvement from initial testing to one month after transplantation on the performance IQ and full-scale IQ (reed 18). The significant difference was not maintained , however , at 1 year after transplantation .The later the onset of renal failure or the fewer the years in ESRD the less the impairment in cognitive performance. Blood urea nitrogen, serum creatinine levels and blood pressure did not correlate with any of the cognitive or academic achievement measures. In our study too we did not find any such correlation (Ryan et al, 1980) compared patients on dialysis with a group of medical –psychiatric patients. They reported that renal cases showed greater deficit on object assembly and block design subtest relative to neurological cases or medical .Psychiatric patients. Thus, it appears that block design is a sensitive indicator of dysfunction in renal disease. Analysis of the clinical scales of LNNB revealed significant differences between the patients before and after renal transplantation (table7) in motor functions, intellectual ability, expressive and receptive speech , reading , memory and visual functions.

It appears that the language functions are impaired in patients with ESRD .We were

unable to come across any study in the literatures where LNNB has been applied

The Halstead Retain Bsttery was administered by Souheaver et al, 1992 to 24 patients with advanced renal failure , 24 patients with neurological disorders , and 24 patients with medical and or non psychotic psychiatric condition .Their results indicated that the ureamic and neurological group was equal in the overall level of neuropsychological impairment and that were significantly more impaired than the medical-psychiatric group. However, the uremia group showed a pattern of deficits that was qualitatively different from both the neurological and medical – psychiatric groups. In a further study the group also compared patients on chronic haemodialysis with undialysed patients with uraemia and a third group of medical – psychiatric patients. The three groups of 16 patients each did not differ significantly in age, education, verbal intelligence, or degree of affective disturbance .Halstead – Reitan Battery subtest comparisons demonstrated that dialysis patients performed significantly better than uraemic patients and were equivalent to medical-psychiatric subjects on tasks of psychomotor problem–solving and spatial ability .Dialysis patients were impaired relative to medical psychiatric patients on a task of flexible thinking . Dialysis patients were impaired relative to medical-psychiatric subjects and equivalent to uraemic patients on tasks which required complex analysis, auditory information processing, language capacities and sensory –perceptual functions. The impairment of language functions observed by the authors seems to be part of the uraemic process; which does not improve with dialysis .Pliskin et al, 1996 in a similar study comparing 16 well dialyzed patients with 12 controls did not find any significant difference. However. they noted a significant deficit in language ability and intelligence in patients who scored well above the median on the BDI .In our study, we also attempted to find out the effect of depression on the intellectual and neuropsychological functions by doing a correlation study of the BDI score with the performance IQ and the clinical subscales of the LNNB before and after renal transplant (table 8).

However, the BDI did not correlate with any of the subscales of the LNNB both pre and post-transplantation. Analysis of results on the Life satisfaction scale (table 9) showed that the majority in both the pre-transplant as well as the post-transplant groups scored in the high range .None of the patients scored low on the Life satisfaction scale. This is surprising especially as patients with .ESRD undergo considerable stress due to the diseases. Probably the support extended by the service in the form of attachment to the nearest unit in the station having a renal transplant facility , the availability of out-of-turn accommodation on medical grounds , continuation of employment and free – hospitalization play a major role in achieving high scores on the Life satisfaction scale . Also, this may be a cultural variant where our patients seem generally satisfied with their lives notwithstanding the problems they face. We administered the Life satisfaction scale that seemed to answer the question about the quality of life satisfactorily. Quality of life has been linked to outcome in various studies. However, with our patients being generally satisfied with their lives, this finding could not be corroborated. Religious beliefs may also act as coping

mechanisms and help in improving the quality of life in these patients.

Conclusion

Neuropsychiatric evaluation of patients with ESRD on haemodialysis before and after transplantation revealed that 86.7% of the population was depressed before transplantation .Depression was significantly ameliorated in the post-transplant The BDI ii was found to be a sensitive and effective tool for detecting depression in this population. Significant differences were observed in the IQ performance as well as the language subscales of LNNB before and after transplant. Life satisfaction scores also showed a significant improvement following renal transplant.

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Authors

Eltaweel M
Lecturer of psychiatry
Cairo University

Ali H.
Lecturer of Nephrology
Hamd El Essa Organ Transplant Centre (O.C.T Kuwait)

Address of Correspondence:

Eltaweel M
Lecturer of psychiatry
Cairo University

الجوانب النفسية لمرضى الفشل الكلوى المتأخر
مقارنة التغيرات المعرفية والمزاجية قبل وبعد عملية زرع الكلى

لقد أظهرت الدراسات الحديثة وجود تغيرات فى الوظائف المعرفية وأعراض إكتئابية لدى مرضى الفشل الكلوى المتأخر وكذلك ممن أجريت لهم عمليات زراعة الكلى. وهناك دراسات محدودة عن مدى التغير فى الوظائف المعرفية والناحية المزاجية فى مرضى الفشل الكلوى قبل وبعد زراعة الكلى. ولهذا الهدف أجريت هذه الدراسة على ٣٠ مريض من مرضى الفشل الكلوى الذين يخضعون للغسيل الدموى فى دولة الكويت حيث تم مقارنة التغيرات المزاجية والمعرفيه فى هؤلاء المرضى قبل شهر وبعد ٣ أشهر من عملية زرع الكلى. وقد أظهرت النتائج أن هناك تحسن ذو دلالة إحصائية فى الحالة المزاجية والقدرات المعرفية مع تحسن فى الاستمتاع بالحياه لدى هؤلاء المرضى.